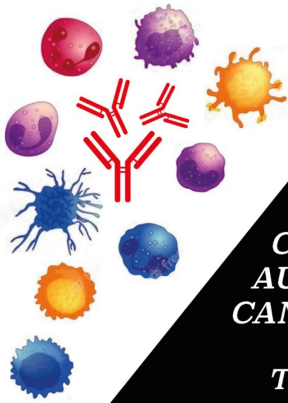
THE PARADOX OF THE IMMUNE SYSTEM



PROTECTION, CHRONIC INFLAMMATION, AUTOIMMUNE DISEASE, CANCER, AND PANDEMICS

The enemy within us

LOUIS J. CATANIA

The Paradox of the Immune System

Protection, Chronic Inflammation, Autoimmune Disease, Cancer and Pandemics

Louis J. Catania

Salus University, College of Health Sciences, PA, United States
University of North Florida, Osher Lifelong Learning Institute, FL, United States

ACADEMIC PRESS
An imprint of Elsevier

Table of Contents

Cover image

Title page

Copyright

Dedication

List of Figures

List of Tables

Louis J. Catania, O.D., F.A.A.O., D.Sc. (Hon.)

Preface

Acknowledgements

Three reasons to understand the immune system

- First…
- Second…
- Third…

Section 1. Our friendly immune system

Section 1 Our friendly immune system

1. Introduction

1. The innate (aka “natural”) immune system and immunity

1. Some simple definitions of the immune system, immunology, the immune response, and immunity

2. Development (embryology and beyond) of the immune system [1]

3. The gross and microanatomy of the immune system

4. Innate (aka “natural”) immune response and active immunity [7]

5. Brief research summaries on the innate immune system

Chapter highlights (key points and paradoxical-related information)

2. The adaptive (aka “acquired”) immune system: from friend to foe

1. The path to “dysregulation”

2. Acute inflammation

3. Clinical considerations in acute inflammation

4. Using the adaptive immune response to help and prevent disease

5. The path to chronic inflammation

6. Brief research summaries on the innate and adaptive immune system

Chapter highlights (key point and paradoxical-related information)

3. Genetics and genomics

1. Introduction

2. Basic science of genetics

3. Immunogenetics

4. Immunogenomics

5. Genetics and genomics by the numbers

6. The Human Genome Project [14]

7. Precision (personalized) medicine and prevention [15]

8. XCI (lyonization)

9. The “microbiome”

10. Epigenetics [26]

11. Cytogenetics

12. Big data analytics in genetics and genomics [32]

13. Brief research summaries on genetics and genomics

Chapter highlights on genetics and genomics

Section 2. The enemy within us

Section 2 The enemy within us

1. Introduction

4. Chronic inflammation: “Enemy #1”

1. Introduction

2. Causes (etiologies) of chronic inflammation [2]

3. Advancing adaptive immunity (from acute to chronic inflammation)

4. Differences in chronic inflammation from acute inflammation

5. Some (but not all by a long shot) disease categories associated with chronic inflammation [7]

6. Clinical diagnosis and treatment of chronic inflammation

7. Neural downregulation of the immune system and chronic inflammation

8. Brief research summaries on chronic inflammation

Chapter highlights (key points and paradoxical-related information)

5. Autoimmune disease: when self becomes the villain

1. Introduction

2. Female predilection for autoimmune disease

3. Theories on the pathogenesis of autoimmune diseases [7]

4. Classification of autoimmune diseases

5. General clinical considerations with autoimmune diseases [21]

6. “Top 10” autoimmune diseases (clinical descriptions, diagnosis, and treatment options) [28,29]

7. General therapeutics considerations with autoimmune diseases

8. Therapeutic (cellular and genetic) procedures

9. Brief research summaries on autoimmune diseases

Chapter highlights (key points and paradoxical-related information)

6. Cancer: immunology's cruelest enemy and greatest challenge

1. Introduction

2. “Cancering”

3. The incidence and prevalence of cancer

4. Description and etiologies of cancers

5. Clinical presentations in cancers [26]

6. Treatment considerations in cancer

7. Brief research summaries on cancers

Chapter highlights (key points and paradoxical-related information)

7. Immunology: The science of pandemics, infectious disease and COVID-19

1. Introduction

2. Background considerations

3. Incidence and prevalence of COVID-19

4. Pathogenesis, immunologic, and immunogenic considerations for SARS-CoV-2

5. Clinical considerations for coronavirus (SARS-CoV-2) infection

6. Immunoinformatics (computational immunology) [68]

7. Epidemiology and public health considerations in COVID-19

8. Brief research summaries on infectious diseases and COVID-19

Chapter highlights (key points)

Epilogue

Glossary

Index

Copyright

Academic Press is an imprint of Elsevier
125 London Wall, London EC2Y 5AS, United Kingdom
525 B Street, Suite 1650, San Diego, CA 92101, United States
50 Hampshire Street, 5th Floor, Cambridge, MA 02139, United States
The Boulevard, Langford Lane, Kidlington, Oxford OX5 1GB, United Kingdom

Copyright © 2022 Elsevier Inc. All rights reserved.

No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or any information storage and retrieval system, without permission in writing from the publisher. Details on how to seek permission, further information about the Publisher's permissions policies and our arrangements with organizations such as the Copyright Clearance Center and the Copyright Licensing Agency, can be found at our website: www.elsevier.com/permissions.

This book and the individual contributions contained in it are protected under copyright by the Publisher (other than as may be noted herein).

Notices

Knowledge and best practice in this field are constantly changing. As new research and experience broaden our understanding, changes in research methods, professional practices, or medical treatment may become necessary.

Practitioners and researchers must always rely on their own experience and knowledge in evaluating and using any information, methods, compounds, or experiments described herein. In using such information or methods they should be mindful of their own safety and the safety of others, including parties for whom they have a professional responsibility.

To the fullest extent of the law, neither the Publisher nor the authors, contributors, or editors, assume any liability for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products, instructions, or ideas contained in the material herein.

ISBN: 978-0-323-95187-6

For information on all Academic Press publications visit our website at
https://www.elsevier.com/books-and-journals

Publisher: Stacy Masucci
Acquisitions Editor: Linda Versteeg-Buschman
Editorial Project Manager: Matthew Mapes
Production Project Manager: Maria Bernard
Cover Designer: Mark Rogers

Typeset by TNQ Technologies

Dedication

For those souls lost during the COVID-19 pandemic and to their families, my deepest sympathy, and to all those in health care and their families who have sacrificed so much, my sincere appreciation.

List of Figures

Figure 1-1 Organs of the immune system.7
Figure 1-2 White blood cells (WBCs or Leukocytes).8
Figure 1-3 Antigen presenting complex (Dendritic cell)—diagram #1.12
Figure 1-4 Early innate immune response—diagram #2.14
Figure 1-5 Continuing innate immune response—diagram #3.17
Figure 1-6 The adaptive (acquired) immune response—diagram #4.19
Figure 2-1 The inflammatory cascade—diagram #5.28
Figure 2-2 Clinical manifestations of acute inflammation—diagram #6.32
Figure 2-3 Treatment considerations in acute inflammation—diagram #7.37
Figure 2-4 Leukocyte (neutrophil) extravasation.38
Figure 3-1 Chromosome.47
Figure 3-2 DNA and RNA structure.48
Figure 3-3 Human karyotype.49
Figure 3-4 Cellular biology of the human genome.50
Figure 3-5 Transcription and translation.52
Figure 3-6 Central dogma of molecular biology.53
Figure 4-1 Acute versus chronic inflammation.75
Figure 4-2 Chronic inflammation and disease.77
Figure 5-1 Clinical autoimmune cycle—diagram #8.100
Figure 5-2 Stem cell renewal and differentiation.133
Figure 5-3 Direct and cell-based stem cell therapy.135
Figure 5-4 Chimeric autoantigen receptor T-cells (*CAART-T*).138
Figure 5-5 CRISPR-Cas9 procedure.139
Figure 6-1 Monoclonal antibody binding to C19 and C3 receptors.164
Figure 6-2 Idiotype-Anti-idiotype Regulatory Circuit (or Loop)—Diagram #9.166
Figure 6-3 Chimeric antigen receptor T-cells (*CART-Ts*).167
Figure 7-1 SARS-CoV-2 life cycle.189
Figure 7-2 mRNA (messenger RNA) vaccine.205

List of Tables

Table 4-1 Theories on etiologies and pathogenesis of chronic inflammation.73
Table 4-2 Proinflammatory mediators.79
Table 4-3 Most common chronic inflammatory orthopedic (musculoskeletal) conditions (Alphabetical).83
Table 4-4 Ten Most Common Chronic Conditions (ranked by death rate).85
Table 5-1 Listing of prevalent autoimmune diseases.98
Table 5-2 Theories on etiologies and pathogenesis of autoimmune disease.98
Table 5-3 Classification of autoimmune diseases by clinical presentation.106
Table 5-4 Examples of biologic immunopharmacotherapeutics.112
Table 5-5 Ten (10) most common autoimmune diseases.112
Table 5-6 Immunotherapeutic medication options for chronic inflammation, autoimmune diseases and cancers (Generic and brand names/… mab suffix = monoclonal antibody).127
Table 5-7 Monoclonal antibody options (generic and brand names).128
Table 6-1 Common cancer types.153
Table 6-2 Top 10 (10) cancers in America.154
Table 6-3 Clinical diagnostic tests for cancer.160

Louis J. Catania, O.D., F.A.A.O., D.Sc. (Hon.)

(Biographical)

Dr. Louis J. (Lou) Catania is an internationally acclaimed educator, and a recognized expert in eye care, health care, artificial intelligence (AI), and immunology. He has authored over 160 journal articles and 12 textbooks, one of which, “Primary Care of the Anterior Segment” received the Baron's Five Star (highest) rating for a medical textbook. He is currently a lecturer with the University of North Florida, Department of Continuing Education, Osher Lifelong Learning Institute; and a visiting Professor at Salus University, College of Health Sciences. During his 52-year clinical and academic career he has taught and lectured extensively worldwide. Dr. Catania's career in health care started as an optometric physician with an interest in corneal immunology. That interest grew into postdoctoral pursuits over the past 35 years with studies in virology, immunology, and public health (University of Rochester, UPenn, Stanford Continuing Studies and MIT OpenCourseWare). He has dedicated himself to research, teaching, and writing with his three most recent books on AI in health care, AI in immunology, and an inspired new text on the mercurial nature of the human immune system (“The Paradox of the Immune System”). Dr. Catania's professional accomplishments in eye care, health care, and immunology have produced countless honors and awards including two Honorary Doctor of Science degrees; Distinguished Faculty Scholar at three academic institutions; induction into the National Optometry Hall of Fame; and innumerable domestic and international keynote and commencement addresses. In his personal time, Dr. Catania is an active volunteer with the National Park Service; a sea turtle patrol monitor in his beach community; and involved in multiple environmental, humanitarian and human welfare agencies.

Preface

Paradox: Something (such as a situation) that is made up of two opposite things that seems impossible but are actually true or possible

Merriam-Webster's Unabridged Dictionary (2021).

The concepts of “self-versus nonself” and “our best friend and worst enemy” are of themselves a paradox. Yet these two apparently contrasting, coupled pairs define the essence of the human immune system. That being so, understanding this biomedical system of inconsistencies requires an appreciation of its components and more so, their relationship to one another. Those intricate and enigmatic relationships represent the science of immunology. They also embrace the inherent evolutionary genetics and human biology that produce and collectively culminate in what this book will attempt to define as “the paradox of the immune system.”

It is not typical to jump to the Epilogue of a book from its Preface, but allow me this brief, albeit unorthodox, digression for what I hope will be a worthwhile departure for you the reader. I start the Epilogue with the question, “So, just what is ‘the paradox of the immune system?’” Then I affirm that “the paradox” is actually a collection of paradoxes, whereupon I proceed to list them (some not all). I am providing this list for you up front so you can enjoy watching the “puzzle” unfold, piece-by-piece (or, if you will, “paradox-by-paradox”) as you read the book. No need to remember them now as I will be identifying them one-by-one as they surface in the narrative:

- Self-versus nonself;
- Innate versus adaptive immunity;
- Adaptive immunity as a friend and foe;
- Our “best friend and worst enemy”;
- Immunity's regulated and dysregulated systems;
- Health protection and health threat;
- Dangerous versus benign nonself and the toll-like receptor (TLR) “sentry”;
- Acute inflammation healing and ulceration;
- Acute versus chronic inflammation;
- Accumulation of immune (cellular and humoral) substances in tissue;

- Tumor Necrosis Factor (TNF-α) inflammatory and antiinflammatory effects;
- Self-versus self (autoimmunity);
- Autoimmunity ("the mother of all immune system paradoxes");
- Female versus male predilections to autoimmune diseases and certain cancers;
- Rogue B-cells attacking self;
- Epitope spreading;
- The role of the X chromosome and miRNA in males versus females;

- Immunosuppressive agents as therapeutics and as threats;
- The immune system and COVID-19 (the infection's best friend and worst enemy).

To achieve the ambitious and unique goal of this book, I will concentrate on a few key objectives. First, I hope to explain in uncomplicated (make that *minimally* complicated), understandable language, the postulate of "self-versus nonself," our first paradox. The "self" part is easy, but "nonself" starts getting tricky along the way as you will see. Second, I must make some sense of, and define the human immune system in its dual role as our (i.e., humankind's) "best friend and worst enemy." As a friend, it protects us 24/7 and helps us defeat the forces that threaten our wellbeing, until…it becomes the enemy itself, and endangers our health and even our lives.

To define "the paradox of the immune system," my plan is to first describe the innate immune system as "our best friend." Then our journey will take us to the darker side of immunology, the adaptive (acquired) immune system. This cryptic, more ominous side includes chronic inflammation ("Enemy #1"), autoimmune diseases ("Enemy #2"), cancer ("the cruelest enemy"), and now, COVID-19. But please understand that the theme of this book and its emphasis on the "evil" side of our immune system is not meant as a negative, pessimistic, or fatalistic discussion of immunology. Quite the contrary. It is an opportunity for us to understand all the dimensions of our ever-present immune responses and the power and control they exert on the human body, for better and for worse. Through such an understanding we are learning how to harness the immune system's biologic potential, both in vivo (within the body) and through medical (molecular biology and genetic) manipulations or "immunotherapies." This leads us to improvements in the health and wellness of the human organism and its ability to fight, cure, and even prevent disease. But notwithstanding the benefits or the potential benefits of the immune paradox, I will also present the challenges we have yet to fully understand. Leading those challenges is autoimmunity, a clinical entity wherein the immune system uses its enormous potential to turn on itself (us) and create clinical disorders like autoimmune diseases and cancers which we have yet to fully understand or conquer.

There is one additional goal I will advance and defend in this book. It is the hypothesis that chronic inflammation, the fundamental immunopathophysiology of the adaptive immune system is in fact, the basis for

all disease (emphasis on *all*). I emphasize *all* because I fully realize that one must not use the word *all* in science or healthcare irresponsibly. In fact, I use it with due respect and regard for its unqualified meaning of the boundless, intrinsic nature of chronic inflammation in the human disease process. I will use the information in the second section of this book, particularly Chapter 4, to defend this proposition. I would even propose a new name, "*pathomelitis*," to better distinguish chronic inflammation from acute inflammation. That may be asking for too much, but what the heck. I do believe a better understanding of chronic inflammation (*pathomelitis*) would lead to a better understanding of immunology and more so, of all disease categories. Just a thought worth contemplating and…prorbably going nowhere.

As to my hypothesis regarding chronic inflammation (*aka pathomelits*), allow me to offer two qualifications that I feel deserve attention, mine perhaps more than yours. The first regards the use of the words "disease" and "disorder." These are two words that will be used regularly in this book (668 times for "disease" and 74 times for "disorder"). I want you to understand their distinction, although somewhat of "a distinction without a difference," as the saying goes. But given the frequency of their use, and my hypothesis about chronic inflammation as the basis of *all disease*, I feel the distinction warrants this brief note. A disease is "an abnormal biological process (a pathology) with a specific cause and identifiable characteristics (signs and symptoms)." A disorder is "…any deviation from or interruption of normal structure or function." [1] I will try to use these two terms appropriately in our discussion, but forgive me if I err once or twice.

My second qualifier regarding my chronic inflammation hypothesis concerns an array of complications (medical, surgical, physiologic, nosocomial, iatrogenic (*bite my tongue!*)) associated with diseases. Unfortunately, those complications are legion and incalculable in health care. They may include cardio or cerebrovascular sequelae like emboli, thrombi, stroke; pulmonary, like pleural effusion, pneumothorax; mechanical, like herniations, obstructions; hematologic like anemias, hypovolemic shock; and on and on. Any theory on disease etiologies must be allowed conditional concessions for such unintended, untoward anomalies. So I hope you'll consider such exemptions as you analyze my thesis. Please!

As you read this book, from time to time you may feel that certain portions are discussed at a more basic level than you would think necessary while other portions may seem more complex. I have attempted to write this book in an expository (descriptive narrative) style to accommodate a range of readers from experienced health professionals to readers with less experience, but no less interested in healthcare matters, especially in this burgeoning area of immunology. Some of the technical information and concepts (some rather complex, I admit), I'll try to present in more straightforward language than technically oriented textbooks. I'll also try to keep things graphic with numerous figures and diagrams ("a picture is worth a thousand words") that will help explain the abundant levels and processes of the complex immune system. I will, however, use technical terms, but hopefully never without having either defined or discussed their meaning prior to their use. I'll use descriptive parentheticals with many technical terms and concepts (there are lots of such terms and concepts, so lots of parentheticals). I am also including a

comprehensive glossary of terminology at the back section of the book for you to reference when needed. But please know that no discussion at any level is intended to be patronizing or condescending, as I hope no one will interpret it as such. It reminds me of one of Albert Einstein's great quotes. *Everything should be made as simple as possible, but not simpler.*

I have included a closing section in each chapter with brief research summaries on the subjects discussed in that chapter. Given the magnitude of the research literature base in all the areas covered in this book, I thought it would be worthwhile to share just a few additional, relevant reviews (67 total). I focus mostly on artificial intelligence (AI) related research for two reasons. First, given a mixed audience of medical and health related readers at all levels, I thought that I should keep the summaries more directed towards applicable clinical studies rather than the heavy-duty biotechnical laboratory research being done in immunology. If a given summary really peaks your interest, I have included reference citations (footnotes) at the end of each so you can use them to obtain the full literature source. Also, please take advantage of the list of technical and healthcare-related search engines I include in my Acknowledgements page for further information on any given topic. (I included these reference resources under Acknowledgements because I wanted to express my appreciation for the enormous value they provided me in my research).

The second reason I focused mostly on AI research is a confession I must make regarding these research reviews. “In the spirit of full disclosure” (ain't that a familiar saying these days?), I must tell you that I have a strong interest and involvement in AI research related to healthcare. I can assure you that some of the best research in immunology and healthcare in general, is now being driven by AI, big data analytics and machine learning algorithms. As such, I do introduce a fair amount of AI technology applications in the research summaries at the end of each chapter.

While AI is not rocket science, it can be challenging without some basic knowledge of its hardware and software. My growing interest in the science (of AI) and my firm belief in its expanding, disruptive nature in all fields, especially in health care and immunology (as the research summaries reflect), led me to write two books over the past 2 years (plenty of time on our hands during the pandemic). The first book, “Fundamentals of AI in Healthcare and Bioscience” (from Elsevier, 2020), introduces AI's increasing role in healthcare. But I do spend the first 3 chapters explaining (trying to, at least) AI basics. If you are not too comfortable or acquainted with AI, it might be of some value to read those 3 chapter (available online) to familiarize yourself with the hardware and software referenced frequently in the research summaries in this book. Of course, there are other sources for basic AI information, but I'm familiar with these 3 chapters and believe them to be an easy, understandable read. The remaining 5 chapters of that first book and the entire second book, “AI in Immunology” (from Taylor and Francis, 2021) go “real deep” into AI's association in health care and immunology and, unless you are a big “fan” of AI, probably deeper than you'd want to go.

Finally, most of my dear friends (and obliging relatives) who were kind enough to do a prepublication review of the manuscript for this book provided

me with a recurring observation. In spite of a logical, steady stream of science and facts throughout the narrative, they indicated that the sheer volume of information was overwhelming. It didn't take much for me to realize that the "steady stream" of information to which they were referring was more like "a fire hose." To wit, I tried numerous times to edit the text (without being "… simpler" per Albert) with a more casual, conversational style. I'm sure, however, many readers will still feel somewhat clobbered by the onslaught of details. So, I decided to do a brief point-by-point summary at the end of each chapter highlighting the most relevant facts and concepts in the chapter with an emphasis (per the book's theme) on the paradoxical nature of the information. I hope that will help anyone "drinking from the firehose."

So, after all is said and done, while it's comforting and hopefully informative to read about and understand our immune system—how it works, how it protects us and helps us maintain health and wellness—we must also try to understand the paradox of why and how it attacks us. After you have read the first section of this book and have become familiar with the immune system as "our friend," you will then be able to better appreciate the effects and issues that chronic inflammation, autoimmunity, cancer and infectious pandemics represent. I will explain those considerations and "try" to help you make some sense of the challenges and the ways we are dealing with them, attacking them, and sooner or later, with the help of modern science and medicine, understanding "the paradox of the immune system."

---

1 Merriam-Webster's Unabridged Dictionary, 2021.

Acknowledgements

Writing a book during an active pandemic on such a timely topic as immunology has proved to be a unique challenge. The constant flood of new information, virtually daily, caused me to have to make additions and amendments to chapter after chapter in order to keep the information up to date. The only way I was able to do that was to rely heavily on the powerful science and medical search engines of PubMed, Medline, and MedlinePlus databases provided by the U.S. National Institute of Medicine, National Institute of Health, Center for Disease Control and Prevention, and by the powerful search engines, Google Scholar, ScienceDirect, Scopus, and others. As with any technical, scientific author, I must acknowledge and thank these resources for providing the current literature base needed to make this book a reality.

Beyond the exhaustive scientific and medical research I did to complete this book, I tried to understand the subject from a personal level as well. To wit, I relied heavily upon many conversations I had with a dear friend who suffers from an autoimmune disease; from multiple friends (and family members) who were infected by the coronavirus; and from two good friends, both now deceased, who suffered through battles with cancer. All of these friends and family members gave me insights into their disease conditions which helped me qualify my discussions, and hopefully provide some empathy to help all of us feel the devastation these diseases bring upon peoples' lives.

Proofing this manuscript was a long and arduous task, one some friends and relatives started but never completed. The ones that did get through it all advised me that the volume of information was formidable and difficult to absorb in one reading. To address this critique, I did a number of adjustments in the text that I describe in the Preface. I thank all of those who advised me on this and helped make a rather complex topic, hopefully a little more “user friendly.” But I must single out one reviewer, Mary Zirakparvar, a scientist herself, who professionally, diligently, and thoroughly proofed the grammar, punctuation, syntax, and mostly, the scientific content for accuracy. Mary made the book better and I deeply appreciate her resolute effort.

My thanks once again go to the professional editing staff of Elsevier with whom I have worked on multiple projects over the years and all of whom have always provided the highest quality service in the kindest, most courteous and most thoughtful manner to a “not so patient” author. My particular thanks for their efforts go to Linda Versteeg-Buschman, the acquisition editor for this book who worked through challenging pandemic conditions to move the book

project forward. A special thank you to the editorial project manager, Matthew Mapes for recognizing the need for a timely, expedited process, given the nature of the book's subject matter relative to the health crisis the world is facing. And finally, my thanks to Maria Barnard, the production manager for a commanding and determined effort to get the job done right; and to Mark Rogers, the art editor for producing a well-designed cover and high-quality illustrations. Overall, it was a first-class effort by a first-class team. Thank you all.

And finally, a very special thanks to my wife, Stephanie, for allowing me the time to do the work and research necessary to complete this book in a timely manner. She understands and tolerates my pertinacious work habits and I love her for that and for the life we have shared together for over 53 years.

Three reasons to understand the immune system

First…

Along with our brain (our central nervous system), our immune system is the apotheosis of our existence.

Understanding it makes us stronger.

Second…

Our human strengths and weaknesses are represented in the “paradox of the immune system.”

Understanding them helps us deal better with our health and our vulnerabilities.

Third…

We all share a sophisticated immune system, its benefits, and its risks.

It is the enduring, unifying system that brings all races, colors, religions, and ethnicities together in one humanity.

Section 1

Our friendly immune system

Outline

Introduction

1. The innate (aka “natural”) immune system and immunity

2. The adaptive (aka “acquired”) immune system: from friend to foe

3. Genetics and genomics

Section 1 Our friendly immune system

1. Introduction

The trendy, overused saying (I already used it once in the Preface, and I'll try to make this is the last) of our times is, “In the spirit of full disclosure….” So…“in the spirit of full disclosure,” I want to admit to you that “immunology and genetics are my passion.” I say that not necessarily because I have devoted the past 35 years (more than half) of my professional life to these sciences that now share a dominant role in health care and the biosciences. Rather, my feelings about these two sciences emanate from what they mean to the human race.

The immune system and its activity is effectively dictated and controlled by the human genome (our complete set of genes). Together they represent the most valuable, sophisticated, and elegant sciences in humankind, ones from which every member of the human race enjoys the benefits. They keep us well throughout our lives and help professionals understand and learn more about how to enhance health and wellness through them. They also protect us from a world of demons (antigens) that endanger our health every moment of every day. And when those demons overwhelm us, all too often with abnormalities like genetic mutations and autoimmune diseases, those very same systems work that much harder to heal us, sometimes successfully and sometimes, not.

This book will limit itself to the immune system alone and its challenges, primarily because, together the sciences of immunology and genetics are just too vast to address in one volume. Nonetheless, the intimate relationship between the two sciences demands that some discussions on genetics related to the immune system (i.e., immunogenetics and immunogenomics) must be included. Thus, along with the immunology concepts we will consider, my approach will be to include genetic considerations where needed in the narrative as well as introduce the basic science and concepts of genetics in a separate Chapter (3) in this Section (1) of the book. This will set the tone and the information needed for our Section 2 discussions about the immune system as “the enemy within us.” Those discussions will include a substantial

amount of genetic science, particularly in the ever-growing fields of immunogenetics and immunogenomics. I hope that the Chapter 3 information on basic genetics will provide succor for you in its Section 2 clinical applications.

Some of my proselytizing about the immune system and genetics in health care may not mean much to you now, but I would ask you to come back and reread this Introduction after you have read the book (I'll even remind you at the end). By then, I think you may love immunology and genetics as much as I do.

1: The innate (*aka* "natural") immune system and immunity

Abstract

Not a day goes by that people aren't besieged by words like antigens, antibodies, cytokines, T-, and B-cells in the media and in conversation. These immunologic terms are not accompanied by simple explanations because these are just not simple concepts. In fact, they're downright complicated and require a careful narrative. And to boot, some of the concepts often include dichotomies, even contradictions that constitute "the paradox of the immune system." The innate and adaptive immune systems are our "best friend and worst enemy." The innate immune system acts as our best friend protecting us and maintaining our health and wellness in the face of constant threats from trillions of antigens ("nonself," foreign substances, and stress). When innate immunity is insufficient to withstand an antigenic attack, the adaptive immune system steps up to help in our protection. The only problem with that is the adaptive immune system, paradoxically, begins to "dysregulate" our immunity and becomes "our worst enemy." This first chapter will present our friend, the innate immune system.

Keywords

Antibody; Antigen; T and B cells; Cytokine; Dysregulate; Innate immunity; Nonself; Paradox; Self; T cells

> *The environment is everything that isn't me.*
>
> *Albert Einstein.*

1. Some simple definitions of the immune system, immunology, the immune response, and immunity

This is a story about all of us, young and old. It actually begins billions of

years ago, but we don't have time to cover the evolutionary trail from the beginning. Rather, let's begin in the 1800s, a mere couple of 100 years ago when gentlemen like Louis Pasteur, Edward Jenner, Elie Metchnikoff, Paul Ehrlich, and others, all considered the "fathers of immunology," discovered and described the cells of the immune system, all of which had been developing over those billions of years that I mentioned. With all due respect to these brilliant "fathers," I am not going to spend much time on them either. Rather, let's fast-forward to the 1970s when another bunch of very bright guys (Ralph Steinman, Niels Jerne, Anthony Fauci [yep, that Anthony Fauci], Peter Doherty, Susumu Tonegawa, and a bunch of other Nobel laureates) started to fill in the blanks that still existed, in spite of, or because of a billion years of development. Today, thanks to the continued flow of gifted scientists and amazing technologies, the Human Genome Project, new drugs, artificial intelligence (AI), and something that has come to be known as immunotherapy, we have arrived at a new level of healthcare. Today, and into the future, our understanding and control of our immune system, as our best friend and sometimes worst enemy, will guide us to better health and wellness.

The immune system is a highly complex system of organs, cells, and chemistry. The study and functions of that system referred to as immunology can be defined simply as a battle of 'self' versus "nonself." In this wonderful world of ours, there is "you" … and everything else. Now, think of "you" as "self" and everything else as foreign to you or "nonself" (those "enemies" I mentioned in the Introduction). Nonself can be a substance (*any* substance), a chemical, an infectious agent known as a pathogen, (e.g., a virus, bacteria, etc.), a toxin (airborne, ingested, in contact with your body, etc.). That nonself can even be a nonsubstance like stress (mental, emotional, physical, as in injury, or physiological—more on this in Section 2). Virtually anything external to you, the nonself-stuff (called an "antigen"), your body (self) interprets as foreign. It's kind of like a "yin and yang" metaphor where self is good and nonself (an antigen) is evil.

Simply stated, the immune response that we'll be talking about throughout the rest of this book is our immune system's reaction to an antigen. That response is our body fighting off the antigen. And that fight is referred to as immunity or simply our body's efforts to overcome antigens and maintain our health. That immunity functions as a natural, inherent process of our body and is called "innate (or natural) immunity." But sometimes our innate immunity is insufficient to overcome an antigen, so it begins to "adapt" itself to function in specialized ways to increase its effectiveness ("gets tougher") and this level is called "adaptive (or acquired) immunity." We're introducing a number of names for immunity here, but from now on we'll stick to innate or adaptive immunity or immune response. In the pages and chapters ahead, we will be spending a considerable amount of time discussing self and nonself, and innate and adaptive immunity, for better and for worse.

2. Development (embryology and beyond) of the immune system [1]

It's fascinating to realize that the immune system is intimately involved in the association of the mother and the fetus during pregnancy. The immune system of mother and fetus is precisely timed to achieve the best outcomes for both. The mother's innate immune system response is aggressive during the first 12 weeks of the pregnancy to support and establish successful implantation of the embryo. The womb is lined with the mother's immune cells and that creates a process called “passive immunity” where chemicals (particularly things like immunoglobulins IgG and IgM which we'll be talking about in a moment) help the fetus get fully established. After that, during the following 15 weeks of the pregnancy, the mother's immune system suppresses itself to allow for the fetal cells to grow as the fetus develops its own immune system (virtually two immune systems functioning in one body). Finally, an aggressive immune system response by the mother returns near delivery, when certain chemicals Mom produces called proinflammatory mediators (more to come on those) help with the labor response.

The womb is a sterile environment and thus no antigens, so the fetal immune system does not need to function. Thus, it is safely suppressed to reduce any potential reactions to the mother's cells which could be interpreted by the developing fetus as foreign (nonself). Meanwhile, fetal cells are crossing the placenta and can be detected in Mom between the fourth and fifth week of pregnancy, and will remain for years, even decades, after she has given birth. The presence of these genetically distinct fetal cells from baby to Mom is called microchimerism (thought to enhance mother's milk). This exchange of cells from the fetus to the pregnant woman provides a possible explanation as to why a mother's immune system does not reject the growing fetus. It's also an interesting phenomenon where the DNA of those fetal cells, male or female, is detectable in the mother (especially her brain) for the rest of her life. This is referred to as “pregnancy brain” and is believed to have lifelong effects (positive, like added protection, and negative, like lifelong potential autoimmune effects in the mother [more on that in Chapter 5]).

Beyond the embryology, after birth the immune system continues to develop robustly until about age seven to eight when it reaches its strongest levels. At that point, general health, proper diet, and exercise will maintain a strong immune system for many years thereafter. But as we age, to be expected as with so many things, the system will begin to slow down a bit in response time and of course, it can be dangerously impaired with any form of immunocompromising disorders (to be discussed in detail in Section 2). But, by and large, the immune system continues to be our principal defense mechanism throughout life, notwithstanding increased risks of certain diseases (e.g., cancers) due to its slower response times with aging.

2.1. X chromosome inactivation (XCI) or "lyonization"

Yet another immunogenomic phenomenon of enormous consequences (as you will read about numerous times throughout this book) is also occurring during early embryologic (preimplantation) development of the female embryo. All normal human beings have 46 paired chromosomes in each cell, of which one pair (the 23rd) is called the sex chromosomes. Females have 2 X chromosomes, while males have one X and one Y chromosome (more on this in Chapter 3). Through a process called X chromosome inactivation (XCI) or "lyonization" (named after the British geneticist, Mary Lyon who hypothesized the theory in 1961 [2,3]), the lyonization theory proposes that one of the 2 X chromosomes in the female is randomly and permanently inactivated ("silenced") in most (but not all) of her cells, with the exception of her lifelong reproductive egg cells. This process prevents female cells from having twice as many gene products from the X chromosomes as males [4]. It provides the upside potential in females for double protection against certain diseases, but it also introduces the increased risk of negative immunogenic influences (in Chapter 5). The overwhelming abundance of a unique RNA molecule (microRNA or miRNA) on the X chromosome represents one of the greatest etymological meanings of "the paradox of the immune system."

Without getting any further "into the weeds" (*for now at least)*, let me just say that the X-chromosome has approximately 155 million base pairs (nucleotides), which translate to about 900–1400 genes that account for about 5% of the total DNA of a cell versus the Y chromosome at about 70 genes and carries about 58 million base pairs or about 2% of the total DNA of a cell [5]. As will be discussed in Chapter 3, the transcription and translation of proteins by the genetic code of these genes (you can take a peek at Fig. 3.6 if you would like a preview) will have dramatic implications in phenotype (physical traits) development, immunity, autoimmune diseases, and cancers. We will elaborate on this exquisite and multidimensional process in our discussion about chromosomes, the microbiome and its association with autoimmune diseases (especially in females) in Chapter 3; again, regarding the X chromosome, microRNA and their association with autoimmune diseases in Chapter 5; and finally, about their role in cancers in Chapter 6.

3. The gross and microanatomy of the immune system

Now for some basic biology of the immune system, the components of which are not too difficult to follow, but worth enumerating because they create a complex network. The involved organs of the body can be considered the gross anatomy of the system. The array of cells, chemicals, molecules, and proteins of the immune system are referred to as its microanatomy, also referred to as its molecular biology.

3.1. Gross anatomy

The gross anatomy of the immune system comprises a number of recognizable organs in the body, like the tonsils, adenoids, thymus, spleen, lymph nodes, lymph vessels, appendix, and bone marrow. Fig. 1.1 will help you identify these structures, not that you'll need to remember their locations but their functions in the system will pop up somewhat regularly. Most of them are responsible for the development and production of immune cells. The strongest cell-producing organs are the thymus (producing the famous "T" cells, for "thymus") and bone marrow (producing an important white blood cell [WBC], the neutrophil and the all-important "B" cells.–can you guess what the "B" stands for? Sorry, that would be too easy. It actually comes from the "Bursa" of Fabricius, a thymus-like lymphoid organ in birds (that's right, birds!) responsible for the production and maturation of B cells (hematoporesis) and processing environmental antigens. In humans, its equivalents are the tonsils or lymphoid tissue in joints and the intestines [6]. (Hardly of significant importance in this discussion, but a little piece of "fun trivia."). All of these immune organ functions become less productive early in life (remember the peak for the immune system by age seven to eight?) and after that, we depend mostly on the collective organs that comprise the lymphatic system (glands and node throughout our body).

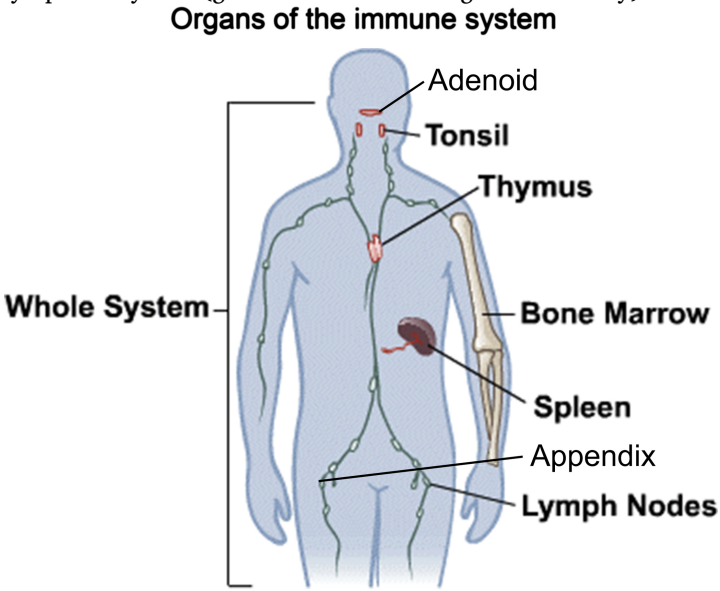


Figure 1.1
Organs of the immune system.A series of bodily organs are most responsible for the development and production of immune cells. The strongest cell-producing organs are the thymus (producing "T" cells for "thymus") and bone marrow (producing neutrophils and "B" cells). Source: AIDS.gov, via Wikimedia Commons.

Besides all of these body organs functioning as the production arm of

immune system cells, the innate (natural) immune system also uses gross anatomical tissues like skin, tears, mucus secretions and mucus membranes in its protective functions. Along with the innate immune cells and an array of molecular biologic agents (to be discussed next), these anatomical tissues serve as a first line of defense against the bad guys (i.e., nonself-invading antigens).

3.2. Microanatomy (molecular biology)

I mentioned the neutrophil just above. This WBC (another name, leukocytes) is a potent immune cell referred to as "the first responder" for good reason as you will see in a moment. But collectively, all the WBCs, particularly the lymphocytes define the critical cellular component of the immune system (Fig. 1.2). Just for the record, let's catalog these cells because you will be running into them again and again from here on out. They are divided into two main types of cells: (1) granulocyte cells (containing small intracellular protein granules) include the lymphocytes or, the "infantry" of the immune system; and (2) agranulocyte cells (no intracellular granules) that include neutrophils, eosinophils, and basophils, residing almost entirely in the blood until they become activated in an immune response. These tough little lymphocytes (very little, from 6 to 14μm in diameter) include T cells, B cells, and natural killer (NK) cells, monocytes, and macrophages (mature monocytes) with about 70% of them residing in the blood (again, until activated) and 30% in bodily tissues. One more granulocyte cell that you will meet again later on is the mast cell (containing histamine and heparin granules) and it resides in connective (supportive) tissue.

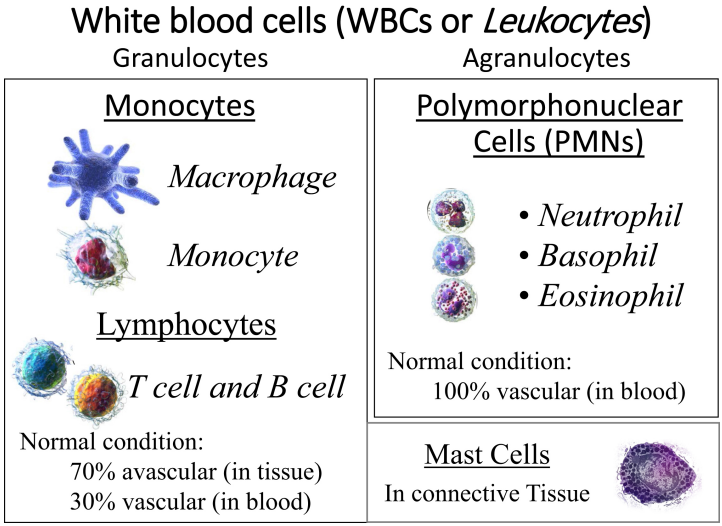


Figure 1.2 White blood cells (WBCs or Leukocytes).White blood cells (WBCs or leukocytes) define the cellular component of the immune system. They are divided into 2 main types of cells: (1) granulocyte cells (containing small

intracellular protein granules). and (2) agranulocyte cells (containing no intracellular protein granules). Source: Louis J Catania © 2022.

Besides the catalog of WBCs that I just hit you with, let me take it one step further. To really appreciate the enormous volume of immune cells in our body, you first have to consider the total volume of all blood cells (WBCs and red blood cells or RBCs), and you have to "think big." The total number of blood cells (and this doesn't include "somatic cells," the kind that make up the bodily tissues) approximates 37–44 *trillion* blood cells (that's with a "T"). Of that number, WBCs represent "only" about 7%–8%, about half of which are neutrophils (so, about 3.5%–4% of the total). Now, if you do the math, that's about 6.5 *trillion* or 6.5×10^{12} WBCs or immune cells (easier to use the exponential form for numbers when dealing with trillions to avoid 12–15 zeros every time). This astronomical number will come back numerous times in our discussion as we consider the actions, reactions, and genetics of the immune system. It's worth keeping it in mind because it helps in keeping the magnitude of the reactions we'll be discussing in perspective.

Up ahead, we're going to discuss, in depth, the immune response with all its cells, chemicals, and proteins. But first, let's consider for a moment that magnitude I just mentioned of what's happening in our bodies. For every antigen we experience in our lifetime (trillions of them), our immune system will produce these protective cells, chemicals, and proteins including antibodies, complement, and/or immunoglobulins plus additional T and B cells, accumulating to $> 2 \times 10^{12}$ over a normal life span. Most of these cells and proteins persist throughout our lives (obviously a good thing, called the anamnestic memory response—more later), that protects us against future attacks by the same antigen. All told, it's really hard to get your head around the size of our immune system.

4. Innate (*aka* "natural") immune response and active immunity [7]

So now we have described the concept of self and nonself and how it defines the basis of our active immune system ("active," yet another immune descriptor). By active immunity, we are talking about the natural or innate actions the immune system (self) conducts in the face of a foreign, nonself attack. At this point, we have already created three labels for an immune response (active, innate and natural), all with the same meaning. We'll be using "active immunity" again in a slightly different context, so, for ease and accuracy of discussion, henceforth, let's use "innate immune response" only (I chose innate vs. "natural" because most of the literature uses innate). Now, let's describe this exquisite innate immune process that everyone reading this book (and in fact, everyone not reading this book as well, or simply, everyone on planet earth) is experiencing, unless they're living in a sterile bubble for protection against antigens (remember the hilarious Seinfeld episode of "The bubble boy"?—

October 7, 1992). But, I digress.

Let's assume you're in good health, well-nourished, in good physical condition with a sound mind in a sound body. You could be sitting in a chair reading (this book) and your body is constantly being bombarded by foreign matter (remember the trillions of antigens I mentioned previously?) in the form of dust, pollen, spores, virtually anything airborne (including your kids and lord knows, all their germs), and probably even some things you're rubbing against (in that chair), or with your hands (and maybe your feet, if its summertime). Your body does not like nonself-antigens, so it is constantly using its innate defenses like the anatomical features (skin, tears, mucus and mucus membranes, antiinfectious barriers, enzymes) and more so, a series of complex cellular and chemical protective elements (coming below, so fasten your seatbelts). That pretty much summarizes the “yin and yang” metaphor we used back on page 4, where “self” is good and “nonself” (antigen) is evil.

4.1. The science of “self” versus “nonself”

Let me apologize in advance for these next few pages as we dive a little deeper into the immune system's parts (anatomy and microanatomy) and its mechanics (physiology and molecular biology). It is arguably the most complex system in our body (neurologists and brain surgeons might argue that point) and its mechanics or its functions utilize a series of cells, molecules, proteins, chemicals, and genes that begin to boggle the mind. So, give these next few pages a shot and maybe even a reread before moving on. I must be honest and tell you that you really have to grasp these next basic concepts to understand the continuing progress of immunity, for better and for worse.

Your body (self) recognizes nonself (antigens) through the series of specialized white blood cells that we've discussed above (WBCs or leukocytes), particularly macrophages, monocytes, and T-lymphocytes (or just T cells). There are a whole bunch of very specialized T cells with surface (protein) receptors that have specific functions. Let's quickly review these T cells and their receptors and then revisit them as their functions manifest in the immune response. The first type is the T helper cells or T_H cells as we will refer to them from here on. The main surface receptors on the T_H cell are human leukocytic antigens (HLAs and more on this in a moment) and CD4, CD8, and others (CD is the abbreviation for “cluster of deviation” or “classification determinant,” a fact that I will not mention again and I suggest you forget immediately, *but not the HLA*). The next T cell is the cytotoxic T cell (T_C henceforth) also called the killer T-cell (no abbreviation on that one) with CD8 receptors (and others); and the T suppressor or T-regulatory cell (T_S or T_{REG}).

There are over 400 known CD receptor on T-cell surfaces and we'll not be mentioning them all (obviously). But I do want to mention just a few others here for a specific reason. These others include CD4, CD28, CD80,

CD86, CD40L, CD99, and CD152 (or CTLA-4) all on the T_H cell and CD8, CTLA-4 (cytotoxic T-lymphocyte-associated protein 4, or CD152) and other receptors on the T_C cell. I mention these extra receptors not to confuse you (Right!), but because they all have a direct link to autoimmune disease and cancer which we'll pick up on in Chapters 5 and 6 and I just want you to be able to make the connection back to this discussion when we get there. So, as you can see, some of these surface receptors can be bad hombres. One of them (appropriately named) is the "programmed death (PD)" receptor (need I say more?). This nasty critter can hook up with a molecule on cancer cells (the PDL or programmed death ligand—a ligand being a molecule that binds to another molecule) and can make some big trouble (like cancers). We'll postpone that discussion to Chapter 6 as well. In the meantime, feel free to forget this bad ("enemy") stuff for the time being. But I think you can already see the paradox between good and evil evolving. Now, back to the good stuff.

4.1.1. Major histocompatibility complex and the antigen presenting complex (APC)

Now, as promised, it's time to introduce genetics into this unfolding story of immunology. I'd almost suggest that you jump to Chapter 3 and read about genetics first and then back to this part, but rather than disrupt this discussion on immunity, l will try to give you just the basic elements you'll need to understand this very important (Nobel Prize level important) immunogenic portion of this immune system process. Then, when you get to Chapter 3, you can refer back if you'd like to review this critical piece of immunology.

The major histocompatibility complex (MHC Class 1 and 2) are a group of genes on everyone's DNA that read (called genetic coding) and interact with surface receptor proteins (HLAs and CDs) to determine self and nonself for that particular individual. The surface MHC gene CD receptors on the macrophage WBCs (uniquely specific to each individual human being) identify antigens specific to that given human being (amazing isn't it? all evolutionary). Upon such identification, the MHC Class 1 and 2 receptors activate and bind the individual's T_H CD cells (MHC Class 1 to CD8 and Class 2 to CD4) to the antigens and the macrophage's surface receptors (this is a process called "the immune synapse," a very, very big deal) to form what is termed an "antigen presenting complex" (an APC—Fig. 1.3—Diagram #1). This APC is sometimes referred to as a dendritic cell because of its microscopic "tree-like" shape.

These APCs (or dendritic cells) are *really, really, really* important because they will dictate most of the immune response going forward. Suffice to say, this concept of MHC genes detecting self versus nonself and guiding the production of specialized, programmed APCs was significant enough to have been awarded the 1996 Nobel Prize in Medicine to Australian, Peter Doherty, who had actually described the phenomenon back in 1974. You have to give it to old Alfred Nobel, actually his Swedish descendants, for owning up and delivering the Prize for this enormous scientific

achievement, even if 18 years later. Better late than never.

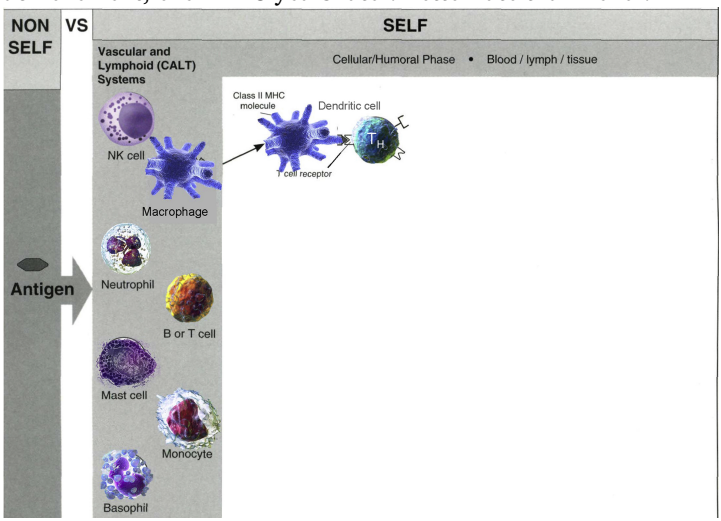


Figure 1.3 Antigen presenting complex (Dendritic cell)—diagram #1.When the human body identifies something as "nonself" white blood cells (macrophages) and T-lymphocytes bind it to form an antigen presenting complex that becomes the starting point for all immune responses. (This figure is the first in a series of 9 diagrams that will ultimately develop an overall flow diagram of the entire immune system).

4.1.2. The "TLR sentry" [8]

There is yet another very specialized protein surface receptor that I must share with you at this time as well. (Now stay with me on this, *please*). It's called the "toll-like receptor" or TLR. This receptor is genetically encoded (programmed) from our MHC Class 1 and 2 genes described above which allow our T cells to do what we've been talking about as the main function of the immune system, that is to distinguish between self and nonself and even between self and self (so that we don't attack and destroy ourselves—*most of the time*—sounds paradoxical doesn't it?). TLRs are particularly good at spotting the real bad guy antigens like bacteria and viruses. So, you can see that this TLR is a big deal in the world of immunity.

An additional characteristic of this elegant antigen recognition system is an interesting feature that allows the T and B cells to determine just how "dangerous" an antigen might be. Is the foreign nonself invader apt to produce an increasing or virulent effect on the human host or is it something the body can tolerate? Indeed, without such a discriminatory capability, the immune system could easily interpret and react to things like ingested nutrients, normal floral bacteria in the gut (the microbiome—more in Chapter 3), digestive bacteria in our intestines, and a world of "benign" foreign substances. Effectively, the immune system could be overworking for no good reason or even for counterproductive reasons

(e.g., attacking normal flora).

The control mechanism to address this immune differentiating capability (yet another paradox) between dangerous versus benign nonself substances (or stress) was again created over hundreds of millions of years through genetic coding of the TLR receptors. These surface receptor proteins are genetically programmed to identify self versus nonself, pathogen versus nonpathogen and also, dangerous versus "tolerable" antigens. With this recognition, the TLR receptors provide the T and B cells with an "attack" or "stand-down" signal. They truly are the "sentry" for the paradox of "self versus nonself." That's a rather sophisticated characteristic of innate immunity, and it only took 500 hundred million years to develop.

A great example of this immune tolerance attribute regards a universally common infectious agent, the herpes simplex virus-1 (HSV-1). Upwards of 90% of all humans are infected with HSV-1 (the more common oral form, that is, the good old fever blister on the lip kind vs. the "not so good" genital HSV-2 form). The HSV-1 virus resides in a latent, inactive form in various nerve ganglia in our bodies. It activates only with additional antigenic stimuli (a trigger), particularly fatigue, stress, illness, menstruation, or exposure to sunlight. This genetic TLR characteristic of tolerance in the immune system explains why "innocent antigens" (like HSV-1) are well tolerated, but do have the potential for activation if provoked [9].

4.2. Active immunity

4.2.1. The first signal

OK. Now we have all the pieces in place to see how this elegant immune system works. This first step in the innate immune response is a really big deal because those APCs (trillions of them) start sending out signals (#1) that are going to produce chemical messengers called cytokines (things like interferon, interleukin—IL1,4,5,6 [Fig. 1.4–Diagram #2] that you've heard mentioned, but never knew exactly what they were all about). Interferon proteins (IFN alpha [A], beta [B], gamma [G], and lambda [L]) are particularly effective cytokine (chemicals) that interact with certain genes (like the MHC Class 2 genes to CD4 receptors) in the early stages of the innate immune response to stimulate the "immune synapse" (the continued formation of APCs). It was demonstrated back in the 1970s that the attack by a foreign substance on normal, healthy cells stimulates an increase in interferon as well as producing an antiviral protein that interferes (ergo, the name "interferon") with the production of viruses. (A little side note on this. You'll notice in the first research Reviews at the end of this Chapter, a malfunction in IFN-1 has been linked to increased severity in SARS-CoV-2 infections). These cytokine proteins also produce a powerful T-cell generator, which along with the APCs and neutrophils enhances the innate immune system, thus creating multiple stimuli to an early and effective immune response, but sometimes with consequences

(might we be seeing the very early signs of the potential "enemy" of our immune system?").

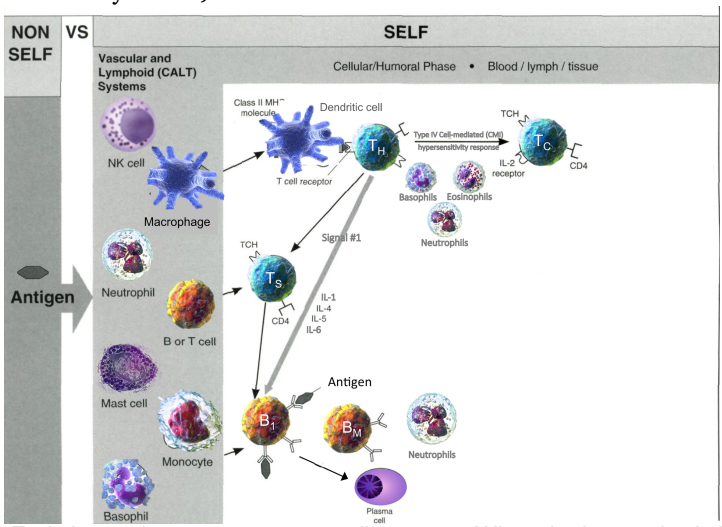


Figure 1.4 Early innate immune response—diagram #2.When the human body identifies something as "nonself" it produces signal #1, a humoral response (cytokines) that elicits B-lymphocytes cells that produce antibodies (classic "Y" shaped icons) which bind and remove the antigen.

Such a potent chemical (humoral) cytokine reaction can produce some inflammatory-like symptoms (to be discussed in Chapter 2), sometimes causing some ill effects in the form of a fever and the patient feeling less than 100% for a few days. But, as we will discuss (in Chapter 2), this is the way the innate immune system works. We sometimes pay a small price to stay healthy (a paradox in itself). Nonetheless, because of its nontoxic, beneficial effects, in the late 1970s interferon became one of the earliest (and highly effective) immunotherapeutic agents used against an array of diseases from infections, to hepatitis, and even to cancers. It had a market value of tens of billions of dollars after its introduction and it is still widely prescribed, especially for certain cancers to reduce the need for chemotherapies and their negative effects (more in Chapter 6). The premise is that Immunotherapies (like interferons) are using the natural body defenses and thus eliminating the effects of toxic chemicals in chemotherapeutic regimes.

4.2.2. The cellular "attack"

Meanwhile, back at the cellular side of innate immunity, those activated T_H cells now begin to show why they are the "infantry" of the immune response. Through the chemical (cytokine) signals being produced (specifically interleukin or IL-4, 5 and 6 from the macrophage on the APC), with the help of WBC monocytes and those powerful neutrophils we talked about earlier (specific for microbial pathogens), the T_H cells proceed

to do one of their most important functions. They activate another group of lymphocytes beyond their T-cell brethren, the B_1 cells. With T_H cells as the "infantry," the B_1 cells take their rightful place alongside the T cells as the "special forces" of the immune system. This B cell begins the production of the "big guns" (alright, enough with the military metaphors already!), the antibodies, the critical protein molecules that will bind with and neutralize antigens. Now, along with the T_H, T_S and B cells, the antibodies, plus humoral enzymes from the neutrophils (neutralizing chemicals to inactivate toxins and infectious agents), those antigens don't stand a chance. They're effectively carried off to lymph nodes where they will be eliminated or destroyed (ingested) through a process called phagocytosis by WBCs. Meanwhile, the T_C cells we mentioned above plus other WBCs (eosinophils and basophils) are digesting and destroying any remaining pathogens (top of Fig. 1.4–Diagram #2) in a process. This is called Type IV cell-mediated immunity (more on this in Chapters 2 and 4).

Together, the T and B cells are constantly manufacturing millions of copies of themselves, all of which continue to recognize and wipe out the offending antigen. You can pretty much see that this aggressive and cumulative process of innate immunity, in and of itself is usually all that's needed to eliminate the antigen. Simultaneously, the B_1 cells are also forming (germinating) a series of B-memory (B_M) cells and a series of plasma cells that will continue to produce even more antibodies (bottom of Fig. 1.4—Diagram #2). The B_M cells create a long-term memory for recognizing the specific antigen they are responding to and henceforth provide (for a lifetime) the anamnestic memory we mentioned earlier. We'll talk more about that in Chapter 2, but I think you can already begin to see the concept of vaccines developing in this beautiful molecular biological process.

4.2.3. The antibody-encoding gene [10]

This description of the B-cell producing antibodies that bind with the antigen bespeaks a simple question. How does that B cell know which antigen it has the capacity to bind to and more so, to destroy? As with many "simple questions" about the immune system, once again, this one has its answer in our human genome (the complete set of genetic information and instructions on how our body grows, develops, and functions). It is all a product of human development (phylogeny) wherein our genetic code has refined itself iteratively over eons of time into trillions of specific cellular characteristics with distinct genetic strands in our B cell genetically programmed to identify antigens it has never previously encounter and produce antibodies that identify and bind to the antigen's surface receptors and destroy the antigen. This is an amazing feature of our genetic code called the antibody-encoding gene, a discovery that won a guy named Susumu Tonegawa the 1987 Nobel Prize for Physiology and Medicine. (Notice how these Nobel Prizes keep piling up as we move further into immunology. And more to come). Basically, this

antibody-encoding gene explains how our immune system protects us against all foreign, nonself antigens, never before encountered by our bodies. Simply amazing!

This discovery has proven to be of enormous value in immunotherapies, vaccinology, transplantation medicine, and especially autoimmune disease (all covered in Section 2). But that is just one facet of the relationship between our immune system and our human genome. As such, as I mentioned in the introduction to this Section, Chapter 3 on basic genetics and our genome will be very valuable in helping you understand a little better, MHCs and those genetic relationships between the immune system and our genome. It will also introduce the basic concepts of immunogenetics and immunogenomics that we are mentioning here in this chapter and will be presenting further in this Section 1 and throughout Section 2. But first let us complete our discussion on basic immunology.

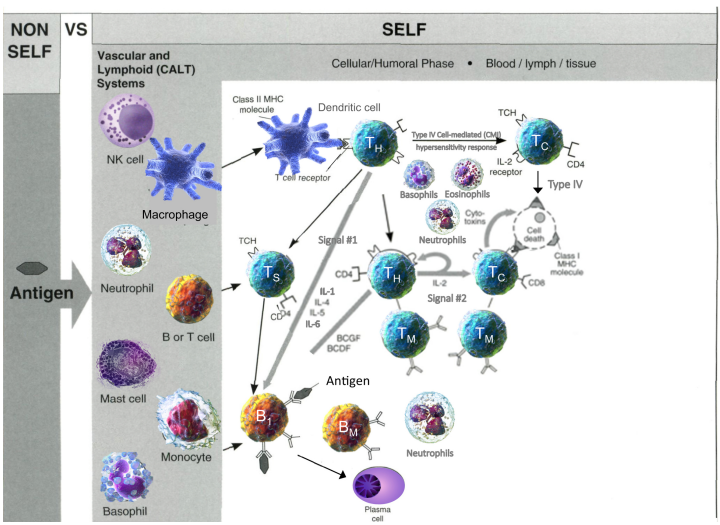


Figure 1.5 Continuing innate immune response—diagram #3.Cytokines (and chemokines) start producing their own biochemical signals (#2) that trigger a new series of T_H, T_S (obviously the cells that will be controlling and "suppressing" the reaction) and T-cytotoxic (T_C, to assist in destroying the antigen) lymphocyte cells.

4.2.4. The chemical/humoral "attack" (second signal)

As they're released through the cell activity during the immune response, the cytokines and chemokines (another type of chemical) start producing their own biochemical signals (#2) that trigger a new series of T_H, T_S or T_{REG} cells (the cells that will be controlling and "suppressing" or "modulating" the immune reaction), and T_C cells (the cells assisting in destroying the antigen) (Fig. 1.5—Diagram #3). Together this exquisite molecular biological innate immune system process is your body's 24/7 defense apparatus. We might even label it "our best friend." [11] But we're

just beginning.

In a continuum of immune activity, if and when the HLA and TLR receptors recognize greater antigen risk, that is, infectious pathogens versus noninfectious self, they begin to morph or “adapt” into a second innate immune response signal (#2). This involves additional cytokines like interleukins (particularly IL-2 and 6) which stimulate further T- and B-cell production. And all this immune activity is helpful … to a point. Too much of a good thing could turn bad, or even deadly in the form of an autoimmune response (full discussion on this profound paradox in Chapter 5). So, the innate immune system also needs some checks and balances and ironically, they come in the form of the cytokines, especially the interleukins we've been mentioning [12]. Many interleukins (e.g., IL-1) serve as antiinflammatory mediators sometimes called “the brakes on the innate response.” (Inflammation is the next level of the immune system which we'll address in Chapter 2). The lack of these inhibitory antiinflammatory mediators would lead to uncontrolled innate immunity and a progenitor to advancing immunity, autoimmunity (selfattacking self) and its serious, consequential diseases, including cancers which will be discussed in Section 2.

All of these issues needed better understanding and scientific considerations if we were to keep the immune system in balance and provide a homeostatic (balanced) condition in human health. No less, a popular contemporary name surfaced as a key figure in this challenge. Dr. Anthony Fauci stepped up in 1980 and created the National Institute of Health, Laboratory of Immunoregulation. Subsequently, in 1984 he was named the Director of National Institute of Allergy and Infectious Diseases, a position he still holds today along with Chief Medical Advisor to President Joe Biden. I would add here that Dr. Fauci's accomplishments in immunology and Public Health are legendary. His work in monoclonal antibodies, HIV-AIDs, ebola research, autoimmune diseases and certainly, his impassioned efforts during the COVID-19 pandemic has changed the face of healthcare and have made him a hero to many—myself included. There will be more on Dr. Fauci's work in subsequent chapters.

4.2.5. The regulated immune system

Meanwhile, back at innate immunity, cellular elements (B cells, B-idiotype cells, B-memory cells, plasma cells, NK cells) are all continuously generating memory cells for future recognition and an “anamnestic” response to antigens. But more so, these additional cellular and chemical (humoral) elements are generating more and more antibody proteins specific to the invading antigen, along with a very complex complement system of immunoglobulin antibodies (IgA, IgG, IgM). These antibodies are the most common in our body (IgG being the most abundant) and are most important in fighting bacteria and viruses. All of these molecules continue to bind and remove antigens through lysing, opsonization, chemotactic activity and polymorphonuclear phagocytosis. Collectively, we can refer to these well directed, protective immune activities as a “regulated” immune

system (Fig. 1.6—Diagram #4. *Please remember this diagram as it will serve as the basis for* Figures 2.1, 2.2 and 2.3 *in* Chapter 2 *and again in* Chapters 5 and 6 . *Trust me on this. I promise it will make sense when we get there*).

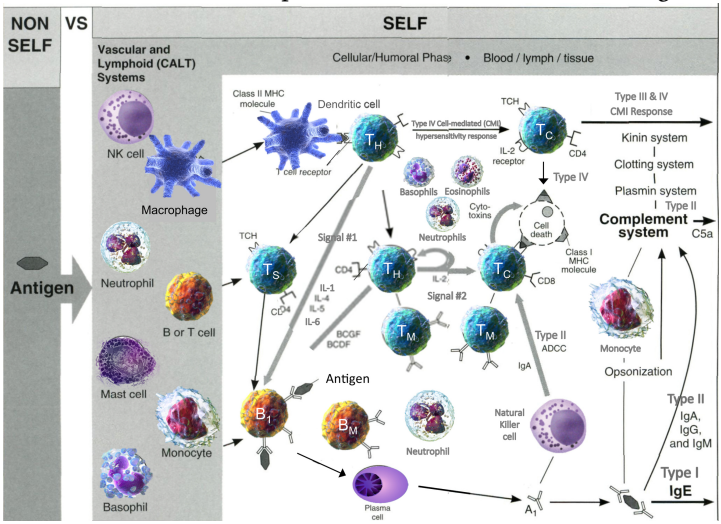


Figure 1.6 The adaptive (acquired) immune response—diagram #4.When the innate immune system is unable to effectively remove the antigen, a complex of events occur producing multiple forms of T and B cells and plasma cells (antibody generating cells), immunoglobulins, natural killer cells, complement proteins and cell-mediated responses to eliminate the antigen.

Driving this constant innate "regulating" process is the powerful neural system's "downregulation" stimuli discussed in Chapter 4, page 87. But, notwithstanding this great "regulated" system (still our friend) and neural downregulation, you may notice in Fig. 1.6 some arrows heading somewhere to the right of the diagram with labels like Type I, II, III, IV. A famous old baseball pitcher, Satchel Paige once said, "Don't look back. Something might be gaining on you." As regards those "arrows," at about this point in the immune system, "something might be gaining on us." We'll be "looking back" in Chapter 2.

4.3. From "regulated to dysregulated"—from innate to adaptive immunity

Now, what if this great and powerful, regulated system doesn't quite do the job of constraining or removing virulent, invading antigens from our body? We'll mention causes in Chapter 2, and you probably know them already: too much antigen; reoccurring antigen (how about smoking as an example?); too powerful a pathogen (novel coronavirus is a good example of that); or maybe, for some reason, our immune system isn't working right (diet, environment [pollution, etc.], genetics)? We're not finished, by a long shot. The indefatigable immune system, in conjunction with the

signal #1 and #2 innate immune response and neural downregulation continue to stimulate an unremitting series of T_H, T_C, B lymphocytes, and cytokines, This generates more antibody-producing cells like the plasma cells, NK and T_S and T_C cells continue to respond to the invading antigen, particularly pathogens like viruses. Meanwhile, immune cells, cytokines, antibody proteins, complement proteins, and debris from apoptotic (dying) cells are all beginning to pile up in our system and, low and behold our own system begins to interpret that abnormal accumulation as “foreign.” Let's face it, all that detritus doesn't belong in normal tissue and thus, our “ying and yang” metaphor is turning into a “who's the good guy and who's the bad guy” antigen-antibody response. To wit, yet another highly complex antibody process starts working.

The combination of all these antigen-antibody generating processes that started with the APC and the innate immune response has clearly graduated or has begun to “adapt” themselves to a new level of immunity. Credit for recognizing and describing this process goes to a brilliant Canadian researcher, Dr. Ralph Steinman for identifying the dendritic cell (the APC) progression from an innate (regulated) immunity into a “dysregulated” immunity. This new level of immunity can be considered a new type of immune response, indeed a dysregulated response. That response is appropriately referred to as the adaptive (or acquired) immune response. While innate immunity continues its robust, protective efforts to defeat “nonself,” a fight it wins most of the time, if it starts losing ground, we begin to rely on yet another, even more potent immune system, adaptive immunity.

So now, with an understanding of the regulated, innate immune system, “our best friend,” let's move on to the dysregulated, adaptive (acquired) immune system (henceforth to be called the adaptive immune system, again consistent with the standard literature's lexicons). In the adaptive immune system, we are introduced to a “friend” to a degree, but at the same time (again, paradoxically) a kind of medical science analog to Robert Louis Stevenson's Dr. Jekyll and Mr. Hyde. Here, the metaphor portrays Dr. Jekyll as our innate immune system or, our “best friend,” while the evil Mr. Hyde corresponds to the equivalent of the adaptive immune system or, “our mercurial adversary.” Yeah, I know, a bit of a dramatic stretch, so you'll have to use your imagination. That's the best I can do for an appropriate metaphor as our paradox unfolds.

5. Brief research summaries on the innate immune system

(Reference citations for each research study presented below can be found in its corresponding footnote. Also, a listing of available scientific reference sources and databases used by the author are included in the book's Acknowledgments.)

1. Notwithstanding labeling the innate immune system “our best friend,” we have to be careful about jumping to conclusions too quickly. Of interest here, is some COVID-19 research that continues to find possible causes to the more severe cases of the novel coronavirus in humans. An interesting finding has come to light regarding one of the innate immune response's interferons (IFN), specifically IFN-1 [13].
   Autoantibodies are antibodies generated by a person's own body rather than in response to an antigen (more on these and on COVID-19 in Section 2). These autoantibodies, found in up to 10.2% of the general population, seem to block or cause a malfunction of IFN-1 and possibly other cytokines. This innate anomaly in IFN-1 has been attributed to at least 3.5% of patients with life-threatening COVID-19 disease. Could this be a sign of the innate immune system also functioning as “the enemy within us?” We'll be discussing that in greater detail in Section 2.
2. Research in the field of immunology (and genetics), especially with the help of AI and our quest to understand infectious disease (for obvious reasons), is rapidly advancing our understanding of the immune system and its clinical effects on our bodies. There will be more discussion of research in Section 2, but let me give you some brief practical examples of the benefits being realized that illustrate the direct value this AI research is having in our lives already. I'll use two quick research studies relative to the innate immune responses to illustrate those values.
   AI is being used in many immunological fields for its analytic abilities for antigen and phenotype (observable characteristics of an individual) detection, predicting prognosis, and treatment outcomes, etc. Algorithms have been developed to predict the outcome of interactions and classification at the immune molecular levels. Phenotype detection is an example of the classification abilities of AI for cellular classification to determine the presence of particular disorders or their outcomes. Potential regulatory mechanisms and identifying immunogenic prognostic markers for breast cancer (BC) were used to construct a prognostic signature for disease-free survival of BC based on using AI algorithms. Differentially expressed immune genes were identified between normal tissues and tumor tissues. The AI survival prediction system identified 17 immune genes as potential prognostic biomarkers that might be potential candidates for immunotherapy targets in BC patients. These AI survival predictive systems will be helpful to improve individualized treatment decision-making [14]
3. As we've discussed, active T cells in our body are capable of destroying antigens. So being able to distinguish active T cells from depleted (thus inactive) T cells is clinically valuable,

especially in cell donors. A form of imaging (autofluorescence) can make this distinction, though difficult, between T-cell activity in a nondestructive manner by detecting changes in the metabolic cell mechanisms (ribosomes, mitochondria, etc.). An AI program using powerful graphic processing units (GPUs) has demonstrated methods that can accurately classify T-cell activity among human T-cell donors. The AI network classifiers were "trained" (millions of image iterations) on nonbiological images (pictures of T cells). Adapting these pretrained AI networks for active versus inactive T-cell classification provided substantially better performance than traditional methods of autofluorescence images alone, thus advancing the science of cell transfer (discussed in Chapter 5, page 134) [15].

Chapter highlights (key points and paradoxical-related information)

1. The concept of self and nonself ("foreign") is the eternal paradox of the immune system.
2. T cells and their surface receptors are the guardians of our health but some are directly linked to disease like the "programmed death (PD)" receptor related to cancer as one example.
3. Toll-like receptors (TLRs) are "the sentry" of the immune system in helping to distinguish between self and nonself.
4. TLRs determine dangerous versus "tolerable" antigens, and provide the T- and B-cells in innate immunity with an "attack" or "stand-down" signal.

5. Antigen presenting complexes (APCs) generate signals (#1 and #2) that produce cells (T, B, plasma, killer and antibodies) and chemicals (cytokine, chemokines, etc.) that can sometimes begin to accumulate and appear as "foreign" to the innate immune system.
6. The normal "regulated" innate immune system can become confused as to "who are the good guys and who are the bad guys?"
7. The system can begin to generate an increasing antigen-antibody response as it interprets "too much self" as foreign.
8. The innate immune system begins to "adapt" to continue providing protection.
9. As part of this "adaptation" an acute clinical inflammatory response develops to defend against too much foreign antigen or too much self ("autoantigen") causing us to usually pay only a small price to remain healthy.

10. But in its effort to protect, the “adapting” innate immune system can “dysregulate” and lead to the “adaptive immune response” and to serious problems.

References

1. Park J.E, Jardine L, Gottgens B, Teichmann S.A, Haniffa M. Prenatal development of human immunity. *Science* . May 8, 2020;368(6491):600–603.
2. Lyon M.F. Gene action in the X-chromosome of the mouse (*Mus musculus* L.). *Nature* . April 22, 1961;190:372–373.
3. Carrel L, Brown C.J. When the Lyon(ized chromosome) roars: ongoing expression from an inactive X chromosome. *Philos Trans R Soc Lond B Biol Sci* . Nov 5, 2017;372(1733):20160355.
4. MedlinePlus, . *X chromosome* . U.S. Department of Health and Human Services National Institutes of Health; August 18, 2020.
5. Easter C. *X and Y Chromosome* . National Human Genome Research Institute; April 4 2014.
6. Ribatti D, Crivellato E, Vacca A. The contribution of Bruce Glick to the definition of the role played by the bursa of Fabricius in the development of the B cell lineage. *Clin Exp Immunol* . 2006 Jul;145(1):1–4.
7. The Innate Immune System, . *Immunopaedia* . 2019.
8. Fitzgerald K.A, Kagan J.C. Toll-like receptors and the control of immunity. *Cell* . 2020;180(6):1044–1066 19.
9. Ma Y, He B. Recognition of herpes simplex viruses: toll-like receptors and beyond. *J Mol Biol* . 2014;426(6):1133–1147. doi: 10.1016/j.jmb.2013.11.012.
10. Lu R.M, Hwang Y.C, Liu I.J, et al. Development of therapeutic antibodies for the treatment of diseases. *J Biomed Sci* . 2020;27:1.
11. Ibid. The innate immune system; n.d. 6.
12. Justiz Vaillant A.A, Qurie A. Interleukin. In: *StatPearls [internet]* . Treasure Island (FL): StatPearls Publishing; January 2021 PMID: 29763015.
13. Meffre E, Iwasaki A. Interferon deficiency can lead to severe COVID. *Nature* . 2020;587:374–376. .
14. Zhang Z, Li J, He T, et al. Bioinformatics identified 17 immune genes as prognostic biomarkers for breast cancer: application study based on artificial intelligence algorithms. *Front Oncol* . March 31, 2020;10:330.
15. Wang J, Walsh A.J, Skala C, et al. Classifying T cell activity in

autofluorescence intensity images with convolutional neural networks. *J Biophot* . August 15, 2019;13(3).

2: The adaptive (*aka* "acquired") immune system

from friend to foe

Abstract

The purpose of the immune system is simple—protect the human organism from foreign (antigenic) invasion and resultant disease. The innate immune response ("our best friend") does a great job of accomplishing that defense under most circumstances. But sometimes, innate immunity confronts an adversary (a pathogen) that overwhelms it and produces a "dysregulated," adaptive immune response. The first clinical effect is acute inflammation with an array of familiar signs and symptoms (pain, redness, swelling, sometimes fever). If not reversed within days to weeks, this negative pathological condition progresses from the acute state to its more devastating successor, chronic inflammation ("our worst enemy"), and the progenitor of *all* human disease. This chapter presents the clinical, histological, and pharmacological stages and basic immunotherapeutic efforts to arrest and reverse the "inflammatory cascade." Unsuccessful efforts allow the adaptive immune system and chronic inflammation to begin an inexorable, pathological course toward autoimmune disease, cancers, and the ravages of infectious pandemics like COVID19.

Keywords

Acute inflammation; Adaptive immunity; Antigenic; Chronic inflammation; Dysregulate; Fever; Pain; Redness; Swelling

> *It's not whether you get knocked down. It's whether you get up again.*
>
> *Vince Lombardi.*

1. The path to "dysregulation"

Wouldn't it be nice if our body won all its battles against antigens? Needless to say, life doesn't work that way. Sometimes, the innate

(natural) immune system can't quite handle the load. Maybe, for some genetic, pathological (disease) or environmental reason (e.g., smoking—I always love to include that) your immune system is compromised ("immunocompromised") or weakened or suppressed ("immunosuppression"). Perhaps the antigen is not being removed effectively (persistent cause—smoking, pollution, allergic to something), or it keeps reoccurring (reexposure) as the innate system tries to eliminate it. Or maybe the antigen is over abundant or too pernicious (virulent) for the innate immune response to overcome it. In such conditions, after a few days to a week of feeling "not so great," the strength of the human immune system begins to demonstrate more aggressive activity called the "adaptive immune response." All in all, this adaptive immune system serves as a powerful defender and protector … to a point.

Adaptive immunity is more vigorous than the innate form. Its intensity and duration are controlled by the patient's genetic makeup (notice how I move from "person" to "patient" about here?). As adaptive immunity advances, it begins to disrupt the homeostasis (maintenance of a stable condition) of your body and your overall immune system. This disruption is also referred to as "dysregulation" of the immune system.

But notwithstanding such disruption, four specific mechanisms that produce positive effects in adaptive immunity are believed to still be at work. First is something called "feedback inhibition" where removal of the antigen reduces its innate immune stimulus and thus decreases production of antibodies and cytokines, effectively reducing and reversing the response. The second is the neuroendocrine and neurogenic pathways that modulate cytokine production and reduction ("downregulation") to control the immune response. This complex neurological control mechanism is the ultimate regulatory hierarchy for chronic inflammation and will be discussed in Chapter 4, page XXX. The third mechanism is when T-suppressor cells (remember T_S, also referred to as T regulatory or T_{reg} cells) reduce T-helper cells (T_H) and thus produce a commensurate reduction in B-cell activity (which is controlled by T-helper cells, as you'll recall from the innate immune discussion in Chapter 1). It's a bit of "connecting the dots," but the result is worth the trip, that is, a reduction in a dysregulated immune response.

The fourth mechanism for reestablishing a regulated immune system is a very complex genetic mechanism creating a system of idiotype antigen-specific B cells called the "Idiotype-Anti-idiotype Regulatory Circuit. This is a process that selfgenerates, through genetic cloning, creating its own immunogenic stimuli that induces anti-idiotype-specific antibodies ("antibodies 1, 2, etc.") that establish the antibody idiotype-specific regulatory circuit. Confused? Don't worry, so are many scientists who have been studying this extraordinary complex process for years. The process remains the center of much immunology research that has far-reaching implications, especially in vaccines and cancer research. Because of its importance and value in infectious disease (i.e., vaccines for pandemics) and its value in cancer research, let's postpone its description here and

revisit this important aspect of adaptive immunity with a fuller discussion (with illustrations) in Chapter 6 on cancer and Chapters 7 (on infectious pandemics).

2. Acute inflammation

Failure to remove an offending antigen in a timely manner, or malfunction of any one of the four mechanisms described above (feedback inhibition, neurogenic modulation, T_S cells, and genetic cloning) can lead to a pathophysiological response (i.e., an abnormal bodily process) resulting in a clinical effect you have heard about and undoubtedly experienced yourself, called acute inflammation. The word "acute" refers to symptoms and conditions of rapid onset and usually of short duration. This "dysregulation" of the immune system could lead to a more prolonged, destructive process referred to as chronic inflammation (chronic simply meaning a prolonged condition). This later level of adaptive immunity, that is, chronic inflammation has potentially devastating consequences and is the process I mentioned in the Preface as the basis of *all* disease. We will be taking this up in detail in Section 2, Chapter 4.

These advancing clinical (inflammatory) effects of adaptive immunity and their various potential endpoints are the next level of active immunity (remember that was the generic term introduced in Chapter 1 for innate and adaptive immunity). So, adaptive immunity represents the second half of our earlier stated paradox about the immune system ("best friend and worst foe"). Adaptive immunity could indeed be considered "our most dangerous foe." (NB: All inflammation, acute and chronic is characterized in medical terminology by the suffix " … i t i s." Thus, any condition mentioned, henceforth, under any disease category with the suffix " … itis" [and there are a lot more of them coming up] should be considered an inflammation.)

2.1. Immunopathophysiology ("dysregulation" and hypersensitivity)

We can look at adaptive immunity as a race to eliminate the bad guy (antigens), a competition which, in most cases (given an otherwise healthy person), the combined innate and adaptive immune systems will win. If, however, the underlying health of the patient is not adequate enough to sustain the activity of the adaptive immune response, things could begin to deteriorate or "dysregulate."

Among the cellular reactions associated with the adaptive immune response (all those T's and B's and so on), there are four classic "types" of "hypersensitivity reactions" (Coomb's Gell classification referred to as Type I to Type IV—remember Fig. 1.6 and Satchel Paige?). These hypersensitivity reactions (also referred to as "overreactions" because the immune system is now beginning to go beyond its basic "protective"

functions) precipitate the next phase of immunity or the “inflammatory cascade” (diagrammed and discussed below in Fig. 2.1). Each overreaction is induced by different types of antigen categories and each characterized by specific cellular responses and “types” of immunoglobulin antibodies [1]. The four types (always designated by Roman numerals—why? I have no idea) include

> Type I: The immediate, allergic (or anaphylactic) hypersensitivity response;
> Type II: The cytotoxic hypersensitivity reaction;
> Type III: The immune-complex hypersensitivity reaction; and
> Type IV: The cell-mediated, delayed reaction

All four of these hypersensitivity reactions (I like the term “overreaction” better because it more accurately describes these reactions, but “hypersensitivity reaction” is the scientifically preferred term, so I'll stick with it … but cheat occasionally with a parenthetical “overreaction” if I think it helps the discussion). These hypersensitivity reactions usually commence during the acute inflammatory stage of the adaptive immune process (which we pretty much described at the end of Chapter 1 (page 20) under the section “From regulated to dysregulated—from innate to adaptive immunity”). Back there we described the more challenging molecular biology of the process which I'm hoping you understood. Now we'll get to the interesting clinical process which you'll be able to relate to far more than the cellular-chemical stuff. This is the manifestation (the pathophysiology) of all that molecular activity. It's the acute clinical phase or the reactions people see (and feel) as their immune system becomes more real to them (and us).

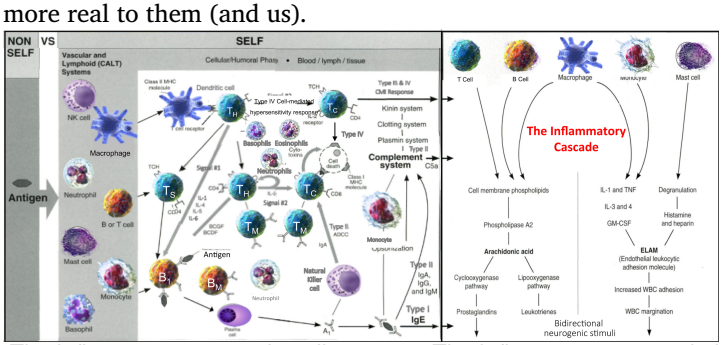


Figure 2.1 The inflammatory cascade—diagram #5.The inflammatory cascade is a pharmacological array of cellular and humoral elements producing a pharmacodynamic process leading to the clinical manifestations of acute inflammation. Source: Louis J Catania © 2022.

But allow me to forewarn you at this point. The more advanced and serious pathophysiological characteristics for each of the four types of hypersensitivity reactions will manifest far more distinctly during the chronic or continuing inflammatory process. I will describe each of the

hypersensitivity types here, but we will be revisiting them in more depth in the discussion on chronic inflammation in Chapter 4. And trust me. Given the magnitude of the chronic inflammatory process on human health, you'll want to understand inflammation at its earlier (simpler) acute phases to better appreciate its profound effects on human health if and when it progresses. So now, given your Chapter 1 basis in the anatomy, physiology, immunology, and pathophysiology of active immunity (remember that generic term for combined innate and adaptive immunity?), let's discuss the nexus between all that immunobiology and the first classic, clinical level of immunology. First some quick descriptions of the hypersensitivity reactions themselves [2].

2.1.1. Type I: the immediate, allergic (or anaphylactic) hypersensitivity response

This is the most common reaction, produced by an antigen referred to as an "allergen." Examples of this response include hay fever, eczema, hives, asthma, food allergy, insect bites and stings, dust, pollen, and on and on. Like its antigen cousin, the allergen can be inhaled, ingested, or enter through the skin. After a susceptible person is exposed to an allergen, the body starts producing a large quantity of IgE antibodies. This results in the reoccurrence of the allergic (anamnestic) response, sometimes with increasing intensity with each reexposure to the allergen. Included among its cytokines, are histamine, eosinophil complement, and heparin, which along with other inflammatory symptoms, produce itching. With the allergic response, symptoms can also include sneezing, and congestion from the release of histamine that is caused by IgE degranulating mast cells (cells that have histamine granules on their surface). In its most severe form, allergic hypersensitivity can produce a life-threatening condition called anaphylaxis (massive accumulation of Type I cytokines) that can cause blood pressure to drop suddenly, and airways narrowing, thereby blocking breathing (anaphylactic shock) [3].

2.1.2. Type II: the cytotoxic hypersensitivity reaction

Type II cytotoxic hypersensitivity reaction (sometimes referred to as antibody-dependent cell-mediated cytotoxicity [ADCC]) involves mainly IgM or IgG antibodies, natural killer (NK) cells and macrophages directed against antigens that cause cell destruction by complement activation (back in Chapter 1, Fig. 1.6). Type II reactions occur within hours of exposure and usually last for a day or so, but could be prolonged. Common forms include blood transfusion reactions and drug sensitivities such as penicillin.

2.1.3. Type III: the immune-complex hypersensitivity reaction

Type III, immune-complex hypersensitivity, is a reaction mediated by the formation of antigen-antibody aggregates called "immune complexes."

These reactions are not mediated by antibodies but rather involve the interaction of T cells, monocytes, and macrophages, sometimes (just to confuse us) also referred to as cell-mediated reactions (Type IV). The reaction can take hours, days, or even weeks to develop (into chronic inflammation), depending on whether or not there is anamnestic memory from previous antigen.

The smaller immune complexes that might become antigen bound to an antibody at the antigen binding site (called an epitope) are not cleared by macrophages and APCs and tend to insert themselves into small blood vessels, joints, and kidneys. These immune complexes can cause an array of symptoms (localized arthus [local vasculitis] inflammatory reactions or urticaria [histamine reactions from degranulated mast cells]. Type III diffuse inflammatory reactions are associated with autoimmune diseases, for example, systemic lupus erythematosus [SLE], rheumatoid arthritis, etc.—see Chapter 5).

2.1.4. Type IV: the cell-mediated, delayed reaction

Type IV, cell-mediated, delayed reaction takes several days to develop and does not involve antibodies. Rather, the reaction involves the activation of phagocytes (pathogen specific), NK cells, antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen (signal #2 in Fig. 1.5 displays this effect). Developing over a two-to-three-day course, in Type IV hypersensitivity reactions CD4 plus T_H cells recognize antigen in a complex with Class 2 MHC (see Chapter 1, page 11) APCs.

This reaction provides immune protection through either humoral (body fluids, serum, and chemicals, e.g., interferons, interleukins—signal #2) or through cell-mediated immunity where the protective immune function is associated with cells. These cells include CD4 cells, NK cells, and helper T_H cells that provide protection against pathogens, and cytotoxic T_C cells that cause death by apoptosis (programmed cell death [4]) without the use of cytokines. Together the reactions are most effective in removing virus-infected cells, but also participate in defending against fungi, protozoans, cancers, and intracellular bacteria. Type IV hypersensitivity also plays a role in temporal arteritis, Hashimoto's thyroiditis, symptoms of tuberculosis, celiac disease, graft-rejection, and chronic transplant rejection.

2.2. The inflammatory cascade

OK, now back to the straight clinical stuff regarding presentations in acute inflammation. Consistent with the definition of its name, acute inflammation and its associated clinical manifestations usually occur within hours to days (minutes in Type I immediate, allergic IgE response) with ulceration occurring shortly thereafter if untreated. Somewhat ironic in this sequence of the clinical inflammatory process is that all of the effects up to (but not including) ulceration, are actually part of the

immune system's healing process (an added paradox of a “best friend—worst enemy” combination!). The adaptive immune response is using many tools, like the cellular components (T and B cells), antibodies, chemicals (cytokines), and more in amounts not normal (“pathophysiological”) to your body. Here, the regular (“physiological”) activity is working diligently to resolve the “pathological” (disease) process in your body. But those valiant efforts are also producing abnormal byproducts like excessive cellular debris and added chemicals called “pro-inflammatory cytokines.” Accumulation of these byproducts is itself a basis for continuation of the acute inflammatory pathophysiological process.

Acute inflammation is a fairly efficient immunopathological defense mechanism of the adaptive immune system. (You'll notice how the “immuno” prefix is beginning to show up in more and more descriptive prefixes, e.g., “immunopathological.” This will be increasing throughout the rest of this book with many more “immuno …” labels. But, I digress—yet again.) This broadly defined, nonspecific, acute inflammatory, immunopathological process produces an observable clinical response referred to as the “inflammatory cascade.”

Fig. 2.1 (Diagram #5) is the continuum or the flow diagram [5] (started with Fig. 1.3 in Chapter 1) that I warned you about (with more to come). The left side of the inflammatory cascade in Fig. 2.1 represents the biochemistry and “pharmacodynamics” (how drugs work and their effects) most associated with acute inflammation and its medical treatments. You'll notice how the drug therapies (corticosteroids and NSAIDs [nonsteroidal antiinflammatory drugs]) produce their effects at particular sites within the pharmacological tree, blocking chemical pathways (phospholipids in the case of corticosteroids and NSAIDs for the cyclooxygenase and lipoxygenase pathways), the chemicals that lead to the dilation of blood vessels (vasodilation or the first level of acute inflammation—see Fig. 2.2) and pain (produced by chemical prostaglandins). Also, the chemicals, histamine and heparin, and mast cell molecule degranulation associated with the Type I allergic hypersensitivity reaction are immunomodulated within this pharmacological tree as well (right side). The balance of the biochemistry and molecular biology on the right side of this pharmacological diagram relate more to chronic inflammation and their relevance will be describe in greater detail in Chapter 4. Also, bidirectional neural stimuli (from innate immunity) continue its downregulating activity which may mitigate or even reverse the inflammatory, adaptive immune activity. But its label, “bidirectional,” also indicates its progressive, neurogenic inflammatory stimuli (discussed further in Chapter 4, page 87).

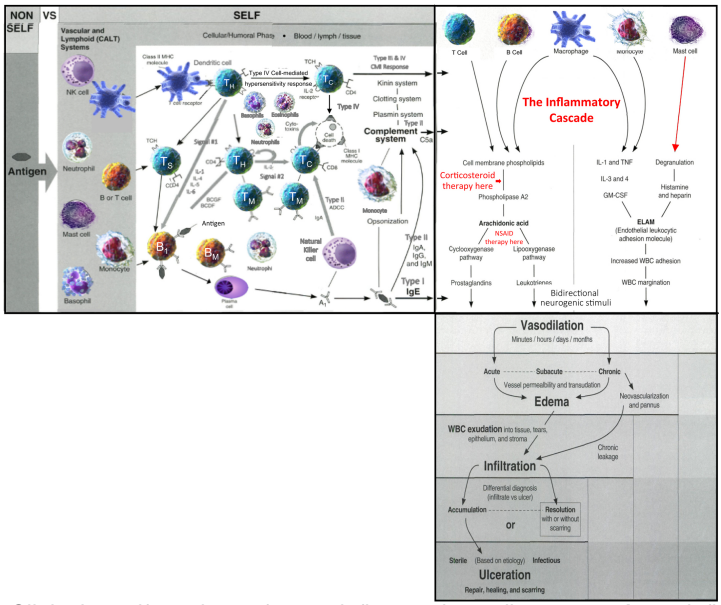


Figure 2.2 Clinical manifestations of acute inflammation—diagram #6.Acute inflammation includes the clinical manifestations of vasodilation (*rubor*), edema (*tumor and dolor*), infiltration (*tumor and dolor*) and, if not timely controlled, ulceration (*functio laesa*). Source: Louis J Catania © 2022.

Acute inflammation can occur anywhere, internally (e.g., acute gastritis, hepatitis, etc.) or externally (e.g., contact dermatitis, keratitis, etc.) producing the inflammatory cascade. The "cascade" includes the pharmacological components producing inflammation and their subsequent clinical manifestations. The pathophysiology and histopathology (tissue reactions) of acute inflammation as defined in the inflammatory cascade are being produced by the cells and mediators of the adaptive immune response (so, believe it or not, all of Chapter 1 does have some relevance) resulting in a dynamic unfolding of clinical events (Fig. 2.2—Diagram #6: the continuum or flow from Fig. 2.1—*I think by now you can begin to see a flow diagram of active immunity emerging from the earliest APC* (Fig. 1.3)*, through innate immunity* (Figs. 1.4 and 1.5)*, then adaptive immunity, and now inflammation* (Fig. 2.2)*. And believe it or not, there's yet still more to come).*

3. Clinical considerations in acute inflammation

The observable signs and symptoms that flow from the inflammatory cascade (Fig. 2.2) are classic and familiar to all of us. We certainly were not the first generation nor even the first (or second) century to recognize or describe them. They are so classic that they were first observed as far

back as 450 BCE and then documented and named by a Greek forefather of medicine, Celsius, in 38 AD (I'll give you the specific names, one by one in the upcoming description. *Pretty excited, I'll bet!*). The classic signs and symptoms of acute inflammation are quite predictable with almost any degree of early inflammation. With proper treatment approaches (described below), unless they reach the level of ulceration, acute inflammation usually diminishes and resolves relatively rapidly with no consequences. When unresolved, due to a lack of timely treatment, no response to treatment or no treatment at all, the condition can spiral into a destructive organ and/or tissue ulcerative process with tissue changes and scarring and more so, into an insidious and destructive chronic inflammatory stage (Chapter 4). But let's assume we're diligent patients. We understand the implications of acute inflammation and mostly, we just want to feel better.

3.1. Signs and symptoms

Acute inflammation is the immune system's attempt to help rather than hurt (as I mentioned previously, a bit of a paradox in and of itself) by reestablishing a homeostatic (stable, normal, balanced) state in the tissue(s) or organ(s) involved. Thus, each of the classic clinical acute inflammatory features has a physiological goal to achieve. Notwithstanding these worthy objectives, these physiological effects produce a disequilibrium (a "dysregulated") subjective (pain and discomfort) and objective (physiologic) response. So, while acute inflammation is trying to help us, we're not all too happy with the help.

We know from our earlier discussion in Chapter 1 (page 13) about active immunity that we need a lot of WBCs (lymphocytes) and their accompanying antibodies to attack and remove antigens. Well, as you recall, most of those WBCs, particularly the neutrophils (remember, "the first responders"?) are in the blood (inside the circulatory system's blood vessels). Upon getting the immune signals from activated macrophages, T_H cells (APCs), inflammatory mediators, cytokines, etc., the main phalanx of cells, countless neutrophils, lymphocytes, and NK cells must now get out of the blood and into the tissue where they are needed. This is accomplished by a process of vasodilation (increased caliber of the blood vessels) that opens the pores in the blood vessel walls. This allows the WBCs to exit the blood vessels (diapedesis—described below) and migrate to the needed area, where the antigen is attacking. So far, so good.

Together, the dilated blood vessels produce redness (*aka* "rubor" from the red blood cells [RBCs]—our first Celsius term) and the increased blood flow creates heat (*aka* "calor"—our second Celsius term). Though poorly understood, it is believed that the inflammatory mediators associated with this adaptive immune response send signals to the brain center (hypothalamus) that controls body temperature. The nervous system sends chemical signals, "dysregulators" that generate the heat to the involved tissue (or organ). Interleukin is a big player in this process (it's called the

“leukocytic pyrogen”). These signals or pyrogenic mediators contribute to the direct calor at the inflammatory site as well as a fever, often associated with inflammation. This is a great illustration of how the immune mediators, especially interleukins and interferons, act as the “wireless” (Wi-Fi, if you will) communication system for immune responses (i.e., nervous system talking to the immune system—see Chapter 4, page 84).

All of this also suggests, as mentioned above, that an overabundance of these mediators and thus, their cumulative stealthy signals, could become overly aggressive and produce an “attack” on the body rather than beneficial, communicating signals. This could generate an antigenic response, or more appropriately termed an “autoantigenic” (signals coming from within the body) response (another immune paradox—seems like they're beginning to pile up since adaptive immunity kicked in). I'll bet you can see where I'm going with that evocative comment. Autoimmunity—“the mother of all immune system paradoxes!” Right on and more on the serious risk of autoimmunity in Chapter 5.

Meanwhile, back at those dilated blood vessels, protein-rich plasma is escaping. While aiding in the tissue defense, that plasma (fluid serum) is also producing edema or tissue swelling (*aka* “tumor”—third Celsius term). There actually is a reason and some good and some bad in this edema effect (usual, when you let nature call the shots). The plasma fluid is loosening the tissue and allowing the WBC cellular elements to migrate more effectively to the antigenic site (that's good) while continually accumulating (*aka* “infiltration”—not so good). Certainly, these plasma and cellular effects are beneficial, but as they accumulate, they also are becoming increasingly more apparent physically (e.g., pus), more uncomfortable to the patient, and more “foreign” (remember, those WBCs don't belong in that tissue, let alone in large quantities). This increasing loss of tissue or organ homeostasis is generating other chemical mediators as well (e.g., prostaglandins) that are increasing pain symptoms (*aka* “dolor”—and that's Celsius' last contribution to inflammation … I think. You never know with these Romans. He probably figured out some way to measure temperature. Naa. That was Fahrenheit, wasn't it?).

Hopefully, all of these activities in the tissue(s) or organ structure(s), especially the potent cellular elements like neutrophil phagocytosis (pathogen ingestion and externally appearing clinically as “pus”) and NK cells along with the T and B cells, are dispatching their immunologic duties of neutralizing the antigen in a timely manner (the mixed leukocytic reaction or MLR). The longer it takes them, however, the more at risk adjacent, healthy tissue becomes as cellular debris and neutrophils begin to interpret otherwise healthy (“self”) surrounding tissue as “foreign.” This possible, idiosyncratic, paradoxical effect can lead to that normal, otherwise healthy tissue destruction and loss, and eventual scarring (*aka* “ulceration”). Along with this tissue or organ destruction (including potential DNA disruptions), permanent loss of tissue or organ function (*aka* “functio laesa”) can occur. So ultimately, what started out as a positive, physiological, mitigating, rectifying immune process, has

become “an enemy within us.”

3.2. Treatment approaches

The variety of treatment considerations (manipulations of the pharmacology in Fig. 2.3—Diagram #7) related to the inflammatory cascade is extensive, but as stated numerous times up to this point, the first treatment is always the removal of the cause (the antigen). Such removal can range from simple hygiene; to antibiotics or antivirals for a bacterial or viral infectious antigen respectively (external or internal) and let's not forget, especially in this age of pandemics, vaccines as anti-virals. Type I reactions (allergy) includes removal of the allergen, antihistamine, decongestants, and mast cell stabilizing drugs. In more severe reactions (including anaphylaxis), topical and oral corticosteroids and injectable epinephrine may be required. In all forms of acute inflammation, cold (wet or ice) compresses are enormously valuable in reducing inflammatory edema by producing vasoconstriction and commensurate reduction in vasodilation of associated blood vessels (i.e., rubor with tumor or edema) that are supplying inflammatory WBCs through the blood vessel wall (diapedesis) to the affected site.

This critically important diapedesis process is instigated by the endothelial leukocytic adhesion molecule (ELAM on the right column of Fig. 2.3). A combination of cytokines induces the ELAMs to stimulate leukocytic (neutrophils in particular) adhesion to the endothelial vessel wall. Then cellular migration associated with surface proteins and chemokines produce blood vessel wall permeability (diapedesis) and extravasation (cell escape from the vessel) of the neutrophils. Fig. 2.4 illustrates this dynamic process. Once outside the blood vessel, as we've been describing, the circulating leukocytes migrate to the disease site(s), where they are activated by various cytokines and chemokines secreted by the macrophages and dendritic cells to help neutralize the antigen. But, without the assistance of removal of the cause by physical or antiinfective therapies, those inflammatory WBCs and chemical mediators become potentially destructive to normal tissue.

Topical and systemic corticosteroids are used to mitigate signs and symptoms in more acute inflammatory reactions (from Fig. 2.2). These drugs produce “masking effects” (reduction of signs and symptoms) but they are palliative rather than curative as is sometimes thought. NSAIDs (nonsteroidal antiinflammatories such as aspirin, ibuprofen, or naproxen) provide pain relief (as antiprostaglandins—from Fig. 2.3). It's also important to remember that as immunosuppressive agents, corticosteroids are reducing the defense mechanisms of the inflammatory reaction and thus its beneficial effects (WBCs, phagocytosis, etc.) against the invading antigen (a therapeutic paradox). When this antigen is an infectious agent, the steroid is reducing its immune mitigation and allowing it to survive, if not proliferate. This also increases the potential for additional opportunistic infectious agents to attack. Thus, corticosteroids have an

attendant risk of secondary and/or increasing infection. Need I say, astute clinical diagnosis and management is essential in all steroid usage. This same risk will be mentioned again in Chapter 4 when we discuss immunosuppressive drugs.

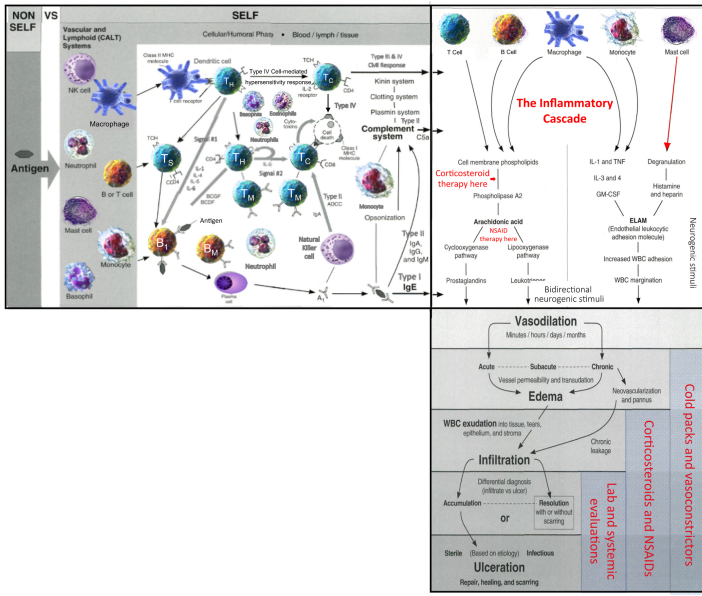


Figure 2.3 Treatment considerations in acute inflammation—diagram #7.The clinical manifestations of the inflammatory cascade (vasodilation, edema, infiltration, ulceration) are treated generically with removal of the cause (antigen); cold compresses (for vasodilation and edema); corticosteroids for infiltration; and aggressive treatments for ulceration). Source: Louis J Catania © 2022.

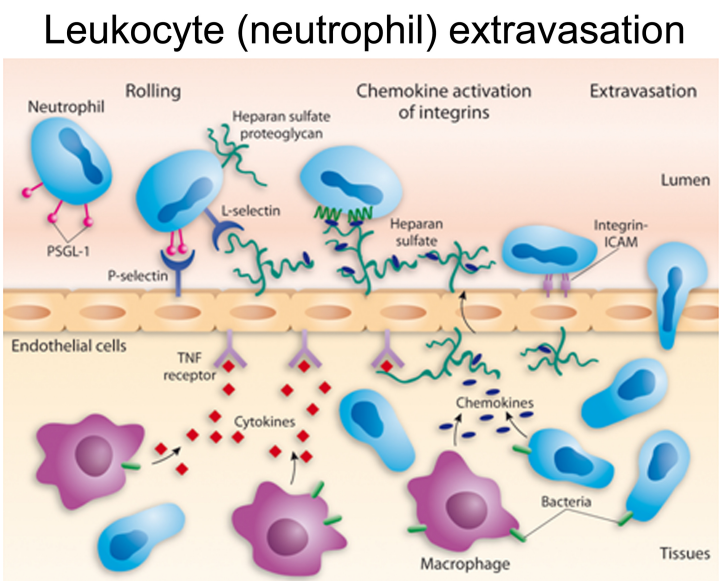


Figure 2.4

Leukocyte (neutrophil) extravasation.Inflammatory vasodilation (redness or *rubor*) opens the pores of the blood vessels to allow WBCs (neutrophils) to "infiltrate" into the tissue (diapedesis) and attack the invading antigen. Source: National Institute of Health, U.S. Dept. of Health and Human Services.

Injury repair and stress reduction (physical, physiological, psychological) therapies are also valuable. Beyond these therapies, treatment is palliative and directed to the involved site (joint, muscle, internal organ, skin, etc.) to reduce the inflammatory process and mitigate the pain (assuming the antigen has been removed). Additional therapeutic measures include nutritional and vitamin supplements, omega-3 sources, compression, stress reduction, and exercise. We can do all sorts of additional chapters (and books) on these "additional therapeutic" measures and their benefits which are voluminous. But I'll have to leave that to other more knowledgeable experts and resources on those subjects. But you really should investigate such measures for improved health and wellness, especially exercise where the literature is exploding on its advantages in sickness and in health.

4. Using the adaptive immune response to help and prevent disease

We have been talking about "our friends," the active, innate, and adaptive immune systems being our defense against foreign, nonself antigens and 99+% of the time doing a great job. In such approaches, we call upon the immune system as we incite, or better still "inspire" it to rally to a preemptive protection against antigens, mostly infectious. The COVID-19

pandemic painfully awakened us to the critical importance of immunology and genetics, especially as we race to find an antiviral drug and vaccines to save humanity. In such cases, we are attempting to modulate, manipulate, and enhance the adaptive immune system to use its powerful cellular and humoral properties to provide a defense against the invading antigen (specifically, the SARS-CoV-2 virus). We might clone neutralizing antibodies (monoclonal antibodies) to bolster the immune attack on the antigen. We might extract programmed antibodies from previously infected patients (convalescent plasma) as preventive therapy. We might try to trick the antigen with modified doppelgangers (copies of itself—in this case, the infectious agent) or introduce an altered form of another viral substance (e.g., an attenuated infectious agent or a recombinant viral vector) to stimulate a controlled production of antibodies to effect an immunity. And thus, we must consider vaccines and vaccination or immunization, (see Chapter 7) a process by which, preemptively (or thereafter) we can beneficially "manipulate" the immune system in multiple ways.

We've gotten substantially better at all these approaches, thanks to dedicated researchers, improved genetic technologies (next-gen sequencing or NGS—see Chapter 3 on genetics), and certainly the help of artificial intelligence (AI) that uses big data analytics (immunoinformatics —see page 210) to search billions of databases for virtually instant answers and expedited solutions. All of these applications of the adaptive immune system to help and prevent disease will be thoroughly addressed in Chapter 5 regarding therapeutic considerations for autoimmune diseases, in Chapter 6 regarding monoclonal antibodies in the treatment of cancers, and in Chapter 7 regarding immunotherapies for COVID-19. But I felt it would be worthwhile during this basic science discussion on adaptive immunity to accentuate its importance, regarding its value in clinical healthcare. It's kind of a "love–hate" scenario and "rubber meets the road" analogy regarding the benefits we enjoy from adaptive immunity and receive as patients from the work the basic scientists provide.

5. The path to chronic inflammation

Through proper diagnosis and removal of the cause, adaptive immunity paradoxically can remain a human biological "friend." Such immunity's clinical manifestation of acute inflammation, in spite of a little discomfort, will usually result in health and wellness. But, if not managed, controlled, and resolved within a reasonable period of time (weeks to months at most), the adaptive immune system can advance to a condition called "chronic inflammation" or truly, "Enemy #1." This form of inflammation differs from acute inflammation as we mentioned in the beginning of this chapter, in its cellular pathology and clinical symptoms ranging from nothing at all to those of acute inflammation and much worse. To further confuse the issue, it should be noted that, though poorly understood,

chronic inflammation can also develop spontaneously, that is without an apparent antigen and acute inflammatory precursor episode.

The development of chronic inflammation could reasonably be considered an advanced form of acute inflammation. But its pathogenesis, histopathology, immunochemistry, and most of all, its clinical course contradicts such a clinical evolution. Rather, chronic inflammation provides irrefutable clinical confirmation that it is a distinct and unique clinical entity, notwithstanding the name it shares with acute inflammation. At the point of clinical diagnosis of chronic inflammation, we can no longer consider the immune system "a friend." We are now faced with the dark side of our immune system, or "the enemy within us." That discussion begins with chronic inflammation (Chapter 4) as a distinct and separate disease entity, while often evolving from its "distant cousin," acute inflammation. Chronic inflammation now devolves into an array of serious abnormalities from autoimmune diseases, cancers and beyond which we will address in Section 2, "The enemy within us."

But first, as promised, in the Introduction to this Section 1, I want to set the tone and provide information needed for a full understanding of Section 2 discussions. This last chapter in Section 1 (Chapter 3) will introduce, in rather abbreviated fashion, the basic science and concepts of genetics, specifically immunogenetics and immunogenomics. This will lay the groundwork for the substantial amount of genetic science that will appear throughout Section 2. My hope is that the Chapter 3 information on genetics will provide comfort for you in its Section 2 clinical applications. I know we can get through this together, so let's keep going.

6. Brief research summaries on the innate and adaptive immune system

(Reference citations for each research study presented below can be found in the corresponding footnote. Also, a listing of available scientific reference sources and databases used by the author are included in the book's Acknowledgments.)

As described in Chapter 1 on innate immunity, research in the field of immunology (and genetics), especially with the help of AI, is rapidly advancing our understanding of the immune system and its clinical effects on our bodies. Here again, research regarding adaptive immunity will give more practical examples of the benefits to humanity being realized through immunology research. The following are three examples of such immunological research.

1. The diagnosis of acute appendicitis is challenging, especially due to the frequently unspecific clinical picture it presents as. Inflammatory blood markers and imaging methods like ultrasound are limited because they have to be interpreted by

experts, yet still do not offer sufficient diagnostic certainty. A recent study presents a method for automatic diagnosis of appendicitis as well as the differentiation between complicated and uncomplicated inflammation using values and parameters that are routinely and unbiasedly obtained for each patient with suspected appendicitis. A total of 590 patients (473 patients with histologically confirmed appendicitis and 117 with negative histopathological findings) were analyzed retrospectively with modern AI algorithms. Results revealed the capability to prevent two out of three patients without appendicitis from receiving “useless” surgery as well as one out of three patients with uncomplicated appendicitis. This clinical study and outcome has the potential to change the current therapeutic approach for appendicitis and it demonstrates the capability of AI algorithms to significantly improve inflammatory disease diagnostics even based on routine diagnostic parameters [6].

2. The inflammatory response runs through all stages of acne. It involves both innate and adaptive immunity. A study aimed to explore the candidate genes and their relative signaling pathways in inflammatory acne used AI data-mining analysis. Aberrant, differentially expressed genes (DEGs) and pathophysiological pathways involved in acne were identified using bioinformatic (AI) analysis. There were 12 DEGs identified and the pathways included chemokine signaling pathway, cytokine-cytokine receptor interaction, and cell-mediated phagocytosis. Discovery of these pathways will serve as a basis for further understanding the pathogenesis and potential therapeutic targets of inflammatory acne [7].

3. Innate and adaptive immune memory is defining features of the adaptive immune system, although their induction is distinctly different. Innate immune memory, sometimes referred to as “trained immunity” is a primitive form of adaptation and provides an increased but nonspecific response to reinfection. Adaptive immune memory is more advanced, with an increased magnitude of response mediated through epigenetic (see Chapter 3, page 62) changes, as well as specific mediation through gene recombination. An integrated model of innate and adaptive immune memory is important for a better understanding of host defense, and for identifying the most effective approaches to modulate it for the benefit of patients with infections and immune-mediated diseases [8].

Chapter highlights (key point and paradoxical-related information)

1. As innate immunity advances to adaptive immunity, “our worst enemy,” immunity moves from “friend to foe.”
2. As adaptive immunity advances, it begins to disrupt the homeostasis (maintenance of a stable condition) of your body and your overall immune system. This disruption is referred to as “dysregulation” of the immune system.
3. Failure to remove an offending antigen in a timely manner or malfunction of any one of four mechanisms (feedback inhibition, neurogenic modulation, TS cells, and genetic cloning) leads to adaptive immunity.
4. This “dysregulation” of the immune system produces the clinical condition of acute inflammation.
5. In dysregulation, there are four classic hypersensitivity reactions (Types I to IV) which induce the ”inflammatory cascade” of biochemical reactions representing acute inflammation.
6. Acute inflammation can be considered a “healing” process through vasodilation, edema, WBC infiltration all of which also produce negative clinical signs (fever, swelling) and symptoms (fever, pain). Furthermore, acute inflammation can become destructive in the form of ulceration.
7. Clinical features of the inflammatory cascade lead to physiological effects producing a disequilibrium and a “dysregulated” immune state.
8. Disequilibrium produces physiological stress and an “autoantigenic” response further disrupting tissue homeostasis.
9. Principal treatment of acute inflammation is removal of the antigenic cause with supportive and palliative (cold compresses, steroids, etc.) measures.
10. Prolonged acute inflammation can lead to the destructive process referred to as chronic inflammation.

References

1. Dispenza M.C. Classification of hypersensitivity reactions. *Allergy Asthma Proc* . November 2019;40(6):p470–473 4pp..
2. Allarakha S, Suyog Uttekar P. What are the four types of allergic reactions? *Med Net* . August 13, 2020.
3. *Allergy and the immune system* . Johns Hopkins Health; 2019.
4. Jorgensen I, Rayamajhi M, Miao E. Programmed cell death as a defense against infection. *Nat Rev Immunol* . 2017;17:151–164.
5. Catania L.J. *Primary care of the anterior segment 2nd edition (textbook)* . McGraw Hill; 1996:22–82 [Chapter 2]. Clinical

Considerations on Anterior Segment Pathology and Immunology.
6. Reismann J, Romualdi A, Kiss N, et al. Diagnosis and classification of pediatric acute appendicitis by artificial intelligence methods: an investigator-independent approach. *PLoS One* . September 25, 2019;14(9).
7. Faria B, Vistulo de Abreu F. Cellular frustration algorithms for anomaly detection applications. *PLoS One* . July 8, 2019;14(7):e0218930.
8. Netea M.G, Schlitzer A, Placek K, Joosten L.A.B, Schultze J.L. Innate and adaptive immune memory: an evolutionary continuum in the host's response to pathogens. *Cell Host Microbe* . January 9, 2019;25(1):13–26.

3: Genetics and genomics

Abstract

Fundamental to "the paradox of the immune system" is human genetics and the human genome. To understand the human immune system and its enigmatic, paradoxical role with our human biology, it is essential to trace its evolutionary history over billions of years. The basic characteristics of the human genome include genes, chromosomes, the deoxyribonucleic acid helix, ribonucleic acid and the "central dogma of molecular biology," protein synthesis, transcription, and translation. These are the building blocks of our current immune system that help us understand the keys to our existence including things like the Major Histocompatibility Complex, Human Leukocytic Antigens, the antibody-encoding gene, base compounds, gene sequencing, and the microbiome ("the second genome"). Understanding these elements of our existence has allowed us to develop the sciences of immunogenetics and immunogenomics and ultimately, lifesaving immunotherapeutics, and genetic procedures including gene editing (e.g., CRISPR-Cas9) and gene transfer (CAR-T cell replacement). A new world coming started a billion years ago.

Keywords

Central dogma of molecular biology; Chromosome; DNA; Gene; Genetics; Genome; Human Leukocytic Antigen (HLA); Major Histocompatibility Complex (MHC); Microbiome; Protein synthesis; RNA; Transcription; Translation

> … *the specific pairing we have postulated immediately suggests a copying mechanism for genetic material.*
>
> *Watson and Crick, The Double Helix, Nobel Prize 1962.*

1. Introduction

Selecting an appropriate placement for this chapter on genetics and genomics related to immunology (immunogenetics and immunogenomics) presented a dilemma relative to the nature of this book. Section 1 is dedicated to the "friendly immune system." It sets the tone and content

necessary to appreciate the adaptive immune system as will be presented in Section 2, “The enemy within us.” But genetic relationships to the immune system play a significant role in both positive (“our friend”) and negative (“our enemy”) aspects of immunology. We've already introduced a number of distinctly positive values of genetics to the immune system (Major Histocompatibility Complex [MHC] genes, CD receptors, antibody-encoding genes, and so on) in Chapters 1 and 2, where more than 20 specific genetic and genomic references have already been made. But coming up here in Chapter 3 and then in all of Section 2, you'll learn more about genetic and genomic affects and the influences they create on immunity relating to chronic inflammation, autoimmune diseases, cancers, and infectious diseases.

Notwithstanding some rather extensive relationships between genetics and the “not so great” effects of the immune system to be discussed in Section 2, I am positioning this chapter on genetics and genomics here in Section 1 for two reasons. First, the nature of human genetics is the basis for the very essence of human life, its form and function, and indeed, its immune defense system. Thus, genetics can be considered perhaps the most distinct and essential feature of our immune system in its positive and “friendly” form. Second, given the frequent, recurring inclusion of genetics in Section 2 discussions, rather than having to describe its science piecemeal with each of its immunologic relationships, let's cover all the basics here and then in Section 2, I'll refer you back to this Chapter (3) when necessary (fairly frequently). I hope this makes some sense to you and that it proves to be a comfortable and efficient approach for understanding this, yet again, complex subject.

2. Basic science of genetics

Nearly three-quarters of our immune system is influenced by genes [1]. Immunogenetics is the branch of science that explores the relationship between the immune system and genetics. Our understanding of how the human immune system functions in health and disease is broadening with the intersection of immunogenetics and the emergence of immunogenomics, the study of the total human genome, or the complete set of genetic instructions. Together, immunogenetics and immunogenomics are creating a body of knowledge that is shaping our current and future healthcare. A review of the fundamentals of genetics should give you a good basis for understanding immunogenetics and immunogenomics.

2.1. Structures and functions [2]

A gene is the fundamental physical and functional unit of heredity made up of DNA (deoxyribonucleic acid, the carrier of the genetic code, or genetic information). It is estimated that humans have between 20,000 and 25,000 genes. Every person has two copies of each gene (called

diploid pairs), one inherited from each parent. Most genes are the same in all people, but a small number of genes (less than 1% of the total) are slightly different between people. Alleles are forms of the same gene with slight differences in their sequence of DNA base compounds. These small differences contribute to each person's unique physical features (their phenotype).

The human body is composed of trillions of cells (Here we go again with "trillions" of things. Almost sounds like a government budget, or worse, a government deficit). In the nucleus of each cell, the DNA molecule is packaged into thread-like structures (helixes) called chromosomes (Fig. 3.1). Virtually every single cell in the body contains a complete copy of the approximately three billion DNA base compounds or nucleotides (exomes) usually designated as letters (adenine [As], thymine [Ts], guanine [Gs], and cytosine [Cs]). In normal genes, these compounds are paired with adenine bound to thymine and guanine bound to cytosine. Collectively, these nucleotide pairs (the exome) make up the total genes of the human genome or the genetic code (By the way, the total genes and proteins that make up the immune system are called the immunome [3]—need I suggest you remember that?).

Corresponding to the double-stranded DNA (helix) molecule is the single-stranded ribonucleic acid (RNA) molecule (much shorter than the DNA strands) (Fig. 3.2). RNA's function is to act as a messenger, carrying instructions (code) from DNA for controlling the protein synthesis (the "central dogma of molecular biology"—more below). RNA also has four base compounds, three similar to DNA (As, Cs, and Gs) and the fourth, thymine (Ts), replaced by uracil (U). In DNA translation (discussed below), uracil replaces thymine to bind with adenine. Stay with me on this. We're getting to some important stuff.

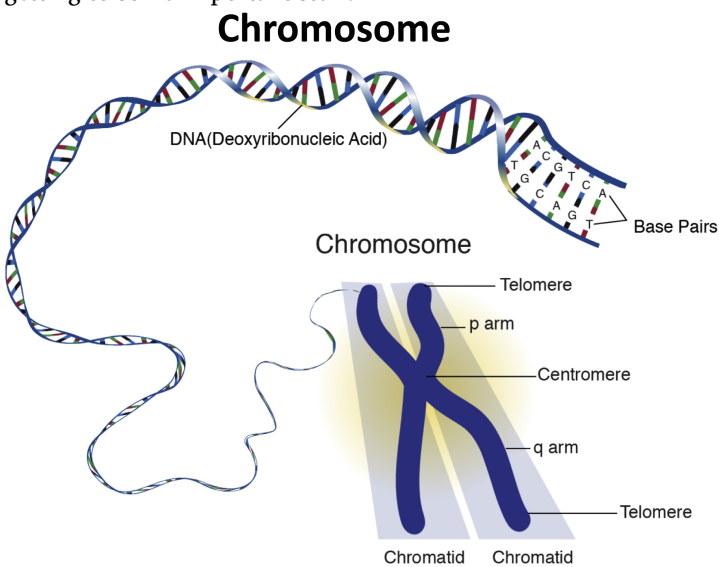


Figure 3.1 Chromosome.In the nucleus of each cell, the DNA molecule is packaged into

thread-like structures called chromosomes. Within each DNA helix are “sequences” (“genetic code”) made up of four nitrogen base compounds, paired as “base pairs” (adenine paired with thymine and guanine paired with cytosine). Together, a base pair along with a sugar and phosphate molecule is called a nucleotide. Source: National Institute of Health, U.S. Dept. of Health and Human Services.

At the ends of each chromosome are stretches of DNA called telomeres (Fig. 3.1). These "tips" of the chromosome are tightly packed chains of nucleotides that degrade slowly over the years resulting in telomere shrinkage. Eventually, their DNA can no longer divide and they become inactive or "senescent" and die. This process is believed to be the etiology of aging. It also has been associated with cancer and a higher risk of death. Also, each chromosome has a constriction point called the centromere that divides the chromosome into two sections, or “arms.” The location of the centromere on each chromosome gives the chromosome its characteristic shape and is used to help describe the location of specific genes. The overall number and shape of all your chromosomes are called your karyotype (Fig. 3.3). Your genotype is the genetic information you carry for a trait, and your phenotype is how that trait is physically manifested on and in your body. Does that sum up all of genetics? Not quite!

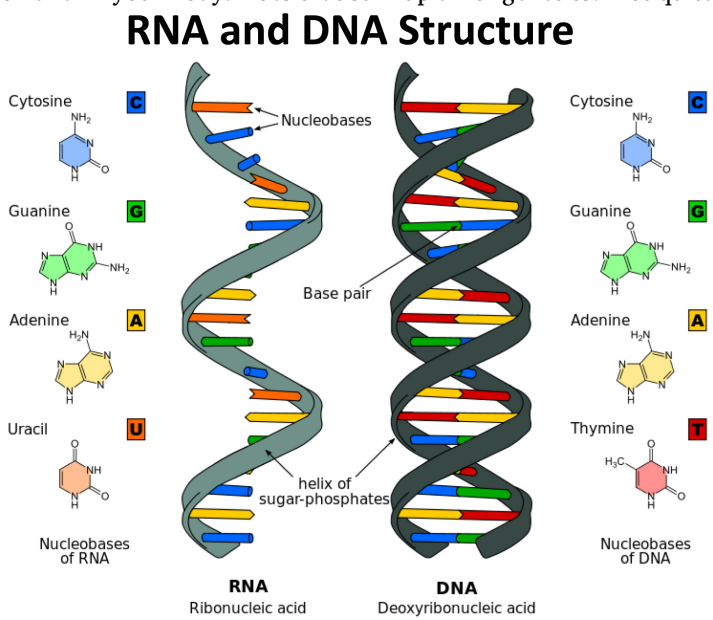


Figure 3.2

DNA and RNA structure.DNA (Deoxyribonucleic acid) is a double-stranded molecules (double helix) with four nucleotides (Adenine (A) pairs with Thymine (T). RNA (ribonucleic acid) is a much shorter, the single-stranded molecule with Uracil (U) replacing thymine. Source: National Institute of Health, U.S. Dept. of Health and Human Services.

Genetics is defined as a branch of biology (molecular biology) concerned

with the study of genes, genetic variations, and heredity in organisms [4]. Genes express (through alleles) specific traits called the phenotype that may be physical (e.g., hair, eye color, skin color, etc.), while others may carry the risk of certain diseases and disorders that may be passed on from parents to offspring. Thus, genetics is the study of heredity, or how the characteristics of living organisms are transmitted from one generation to the next via DNA or your genetic code. Along with immunology, it is this bioscience that has the highest potential of influencing virtually every category of health, wellness, and prevention.

There are a number of elements that make up what is referred to as the molecular biology of genetics or molecular genetics. They include the cell, its nucleus, chromosomes within the nucleus, the DNA strands within the chromosomes, and the base compounds of the genes within the chromosomes (Fig. 3.4). A summary listing of the structures and functions of each part of the genome is as follows:

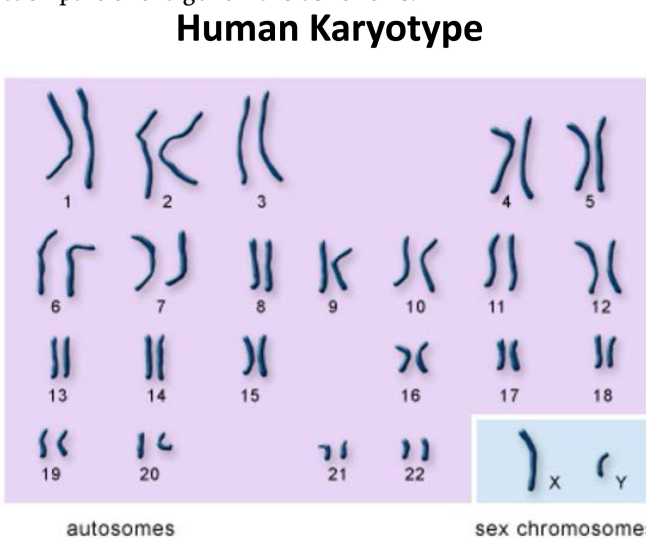


Figure 3.3 Human karyotype.The overall number and shape of all your chromosomes are called a karyotype. Source: National Institute of Health, U.S. Dept. of Health and Human Services.

- The human cell within which is its nucleus;
- Within the cell nucleus reside chromosomes (23 diploid pairs in somatic [body] cells or 23 single haploid strands in embryonic or germ cells);
- Within each chromosomal strand is a double-stranded spiral (helix) of DNA (deoxyribonucleic acid), thanks to James Watson and Francis Crick for this seminal 1962 Nobel prize winning discovery;
- Within each DNA helix are “sequences” (“genetic code”) that represent the order of the four nitrogen base compounds

(nucleic acids), paired as “base pairs” (adenine paired with thymine and guanine paired with cytosine);
- Together, a base pair along with a bonding sugar and phosphate molecule is called a nucleotide (an exon and collectively, an exome);
- These nucleotides are held together by hydrogen bonds and arranged in two long strands that form the double-stranded spiral mentioned above, called the DNA double helix;

The cellular biology of the Human Genome

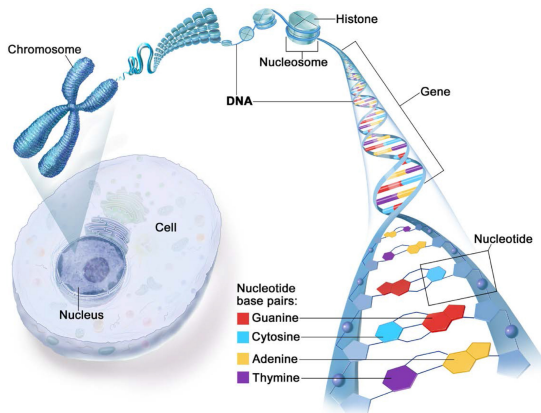


Figure 3.4
Cellular biology of the human genome.There are a number of elements that make up what is referred to as the human genome including the cellular biology of genetics which includes the cell, its nucleus, chromosomes within the nucleus, the DNA strands within the chromosomes, and the base compounds of the genes within the chromosomes. Source: National Institute of Health, U.S. Dept. of Health and Human Services.

- The mapping of these double helixes in the cell of a living organism is called its “karyotype” (see Fig. 3.3);
- Defined groups (from a few hundred to a few million) of these base-compound paired sequences on a DNA double helix are called genes (and once again for emphasis, humans have between 20,000 and 25,000 genes);
- Pairs or series of inherited genes on a chromosome that determine hereditary characteristics (e.g., hair color, eye color, height, etc.) are called alleles;
- The specific makeup and positioning (loci) of these alleles on a chromosome are called a genotype;
- A pair of alleles in the same gene is either autosomal dominant or recessive;
- Homozygous means that both copies of a gene or loci match while heterozygous means that the copies do not match;

- Two dominant alleles (AA) or two recessive alleles (aa) are homozygous. One dominant allele and one recessive allele (Aa) is heterozygous;
- An autosomal dominant allele will always be preferentially expressed (hereditarily) over a recessive allele;
- The visible or observable expression of the results of the genotype, combined with environmental influences (any bodily adjustment to the environment over time), is called the phenotype.

2.2. The central dogma of molecular biology (a *very* big deal!) [5]

Besides heredity dictating the phenotype of the human organism, the critical function of the genetic process and thus, the genes are the production of amino acids. These are the building blocks of the large, complex protein molecules that play critical roles in the structure, function, and regulation of the body's tissues and organs. A gene traditionally refers to the unit of DNA that carries the instructions for making a specific protein or sets of proteins, a process called protein synthesis. Each of the estimated 20,000 to 25,000 human genes in the human genome codes for an average of three proteins.

Located on 23 pairs of chromosomes in the nucleus of a human cell, the genes direct production of proteins with the assistance of enzymes (protease) and messenger molecules (messenger ribonucleic acid or mRNA). Fig. 3.5 presents a schematic diagram of protein synthesis and Fig. 3.6 illustrates the cellular process of transcription and translation (now, here comes the “dogma”).

During transcription, information stored in a DNA's gene sequence (its genetic code) is copied to a smaller, single-stranded ribonucleic acid molecule called mRNA (messenger RNA). The base compounds in the copied DNA, adenine (A), cytosine (C), guanine (G), and thymine (T), form specific pairs with the bases in the mRNA, except adenine (A) in the DNA pairs with uracil (U) in the mRNA (shown is a sequence of three bases called a codon in the mRNA). Then, the mRNA molecule transfers the information (the DNA “code message”) from the nucleus into the cell cytoplasm.

In the next step, translation, mRNA interacts with a specialized complex in the cytoplasm called a ribosome that reads the transcribed DNA code and translates the gene sequence into genetically programmed polypeptide chains that bind together to form amino acids. Finally, in a process called protein synthesis, the mRNA attaches to a ribosome while another type of RNA called transfer RNA (tRNA) assembles amino acid codons that match the mRNA codon sequences and these amino acids bind together in chains to form functional body proteins (tissues, organs, cells, enzymes … you name it). It's important to understand that this process will construct

tissue, cells, etc. from normal, *as well as abnormal* (mutated) genetic code.

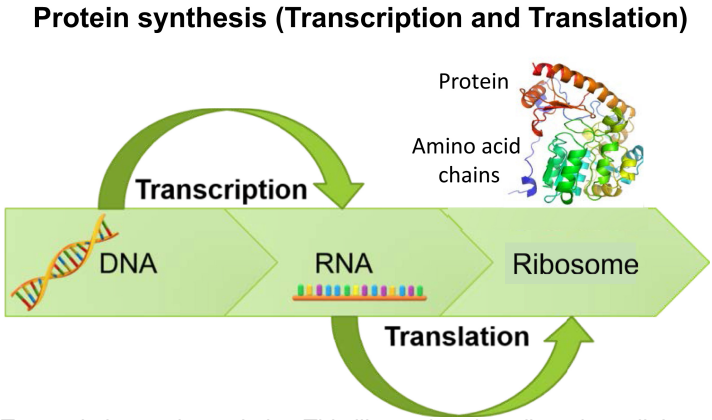


Figure 3.5
Transcription and translation.This illustration describes the cellular process of transcription and translation. During transcription, information stored in a DNA's gene sequence (its genetic code) and copied to a smaller, single stranded ribonucleic acid molecule called mRNA (messenger RNA). Source: Louis J Catania © 2022.

This stepped process (Figs. 3.5 and 3.6) in which hereditary information in DNA is used to make proteins is called the "central dogma of molecular biology" or the science of "transcriptomics." This is what the bioscience of our body is all about. Beyond transcriptomics, which defines the expression of the genes' RNA proteins (the proteome [6]), "proteomics" studies their biochemistry, functions, and interactions within the body. If a cell's DNA is mutated, an abnormal protein will be produced which disrupts the body's usual processes and leads to diseases such as autoimmune diseases and cancers (discussed in Section 2). Needless to say, this genetic process, proteolysis, and protein synthesis will be revisited numerous times in Section 2 in both positive and negative immunogenetic applications.

As mentioned above, other than genetics' phenotype heredity functions, this "central dogma of molecular biology" is the single most important function of our genome. It is in fact, the essence of our being. So, allow me to summarize the steps in the process that builds our body day in and day out, mostly for the better, but sometimes (with genetic mutations), for the worse:

- Transcription: information stored in a DNA's gene sequence (its genetic code) is copied to a smaller, single stranded ribonucleic acid molecule called mRNA (messenger RNA);

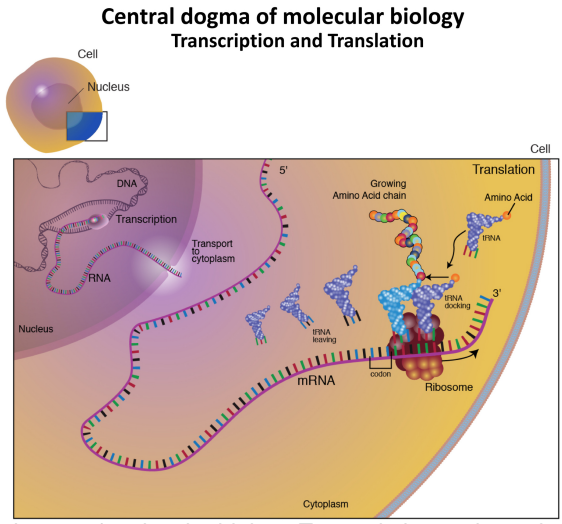


Figure 3.6 Central dogma of molecular biology.Transcription and translation; the top-left part of the drawing shows transcription occurring in the nucleus of a cell: a piece of DNA that codes for a specific gene is copied into mRNA; bases in the copied DNA, adenine (A), cytosine (C), guanine (G), and thymine (T), form specific pairs with the bases in the mRNA, except adenine (A) in the DNA pairs with uracil (U) in the mRNA (also shown is a sequence of three bases called a codon in the mRNA); the mRNA then carries the genetic information from the DNA to the cytoplasm. The right part of the drawing shows translation occurring in the cytoplasm of a cell: the mRNA attaches to and passes through the ribosome; tRNA carries an amino acid to the ribosome, where it binds to a matching codon sequence in the mRNA; the amino acid joins with the other amino acids to form a growing protein chain; the completed protein is then released from the ribosome. Source: National Institute of Health, U.S. Dept. of Health and Human Services.

- These mRNA molecules transfer the information (the DNA "code message") from the nucleus into the cell cytoplasm;
- Translation: mRNA interacts with a specialized complex in the cytoplasm called a ribosome that reads the transcribed DNA code and translates the gene sequence into genetically programmed polypeptide chains that bind together to form amino acids; and

- Finally: In a process called protein synthesis, the mRNA attaches to a ribosome while, another type of RNA called transfer RNA (tRNA) assembles amino acid codons that correspond to the mRNA codon sequences and they join together to form functional body proteins.

It's called "the central dogma of molecular biology," but I like to think

of it as “the bouncing ball of life.” Get it? “Follow the bouncing ball?” … Never mind.

3. Immunogenetics

In our discussion in Chapter 1 about “self” versus “nonself,” the cardinal definition of immunology, we described T and B lymphocytes in some depth. The keys to their immunologic functions centered on their surface receptors including Human Leukocytic Antigen (HLA), CD4 and CD8 surface proteins, and specialized “toll-like receptor” proteins or TLRs (remember “the sentry protein” from Chapter 1?). All of these protein receptors are genetically produced and encoded (programmed) from the Major Histocompatibility Complex MHC (Class 1 and 2) genes. These surface receptors are singularly responsible for the T and B cells' functions of distinguishing self and nonself. The MHC genes are referred to as “the key to self-recognition” and are believed to have evolved (over 500 million years) along with our survival function and our need to reproduce.

MHC genes function similarly within a species (humans), but within the species, there are unique differences between each human being's MHCs such that one human being's MHC can cause rejection of another human's tissue or cells, a challenge in transplantation medicine (page 168). That challenge led to the discovery of the “isoantigens” or HLA genes (mentioned above) that differ within the same species. The 1980 Nobel Prize in Physiology or Medicine was awarded to a French researcher, Jean Dausset for this monumental discovery of MHC and HLA's influences on the origins of our immune system. There will be more about these genes later in our immunogenetic discussion regarding chronic inflammation, autoimmune diseases, and cancer.

4. Immunogenomics

Genomics is a more recently popularized term originating in about 1970 that describes the study of all of a person's genes (their genome), including interactions of those genes with each other and with the person's environment. A genome is an organism's complete set of DNA, the chemical compounds that contain the genetic instructions to develop and direct the activities of every organism [7]. This science deals with the immense volume of clinical material in the human genome through cellular and molecular biology. It is advancing genetic therapies in the study of the human immune system (immunogenomics) and the treatments, cures, and prevention of disease.

Determining the order of DNA proteins (nucleotides) in an individual's genetic code, called DNA sequencing [8], has advanced genetics both for research and clinically. Two methods, whole-exome sequencing and whole-genome sequencing are now being used extensively in health care and research to identify genetic variations [9]. (A compelling example of the value of this science is its use in rapidly identifying coronavirus

variants during the pandemic.) These approaches are known as next-generation sequencing (next-gen sequencing or NGS). The original sequencing technology (the Sanger method) would take months and even years to sequence viral genomes and all of a person's DNA. Next-generation sequencing has sped up the process (taking only days to weeks to sequence a human genome) while dramatically reducing the cost.

In the past decade, there has been a phenomenal change in the efficiency of DNA sequencing. Using traditional methods (Sanger sequencing), the human genome project (HGP) took 20 years and cost $3 billion. Now, next-generation sequencing (NGS—also called massively parallel sequencing) is a high-throughput sequencing using artificial intelligence (AI) big data analytics. This is the method now used to determine a portion of the nucleotide sequence of an individual's genome. It exponentially increases the rate of biological data being generated. From 1990 to the completion of the Genome Project in 2003, DNA-sequencing increased from 1000 base pairs per day to more than 1000 base pairs per second. Whereas the first human genome sequencing (Sanger method) was a $3 billion-dollar project requiring 2decades to complete, as mentioned above, NGS and big data analytics can now sequence a human genome in 24 hours for under $500 [10]. Now that's progress!

5. Genetics and genomics by the numbers

The description of the genetic components and processes, while challenging, is only part of the genetics and genomics story. The more overwhelming feature of these sciences lies in the astronomical numbers their components represent. Those numbers include ~37.2 trillion ($\sim 37.2 \times 10^{16}$) cells in the human body; with ~3 billion (3.0×10^{12}) chromosomes within the nuclei of the cells; with four base compound sequences within the DNA (deoxyribonucleic acid) helixes constituting the 20,000 to 25,000 genes. The number of possible combinations within these sequences (“genetic codes”) of base compounds is astronomical. And yet, it is among these prodigious numbers of gene sequences that congenital (hereditary) and acquired mutations occur [11]. Fortunately, only an infinitesimal amount of them (less than 60 per gene) override “apoptosis” (normal cell's ability to selfdestruct when something goes wrong) to produce genetic disorders or disease [12].

These mutations (structural changes resulting in a genetic variant) are the underlying cause of all abnormalities in human beings. Using the standard advanced algebra factorial formula (you won't be tested on this!), nCr = n!/r!* (n—r)!, for possible combinations, where “n” represents the total number of items (in this case, the number of genes or 25,000), and “r” represents the number of items being chosen at a time (four base compounds), the number of possible mutations in the human genome, spread among 37.2 trillion cells, is 2.5×10^{20} (that's 21 zeros!) [13] plus or minus a couple of million. Locating and identifying those mutations in somatic cells and their clinical manifestations is rather challenging to say

the least. AI and the Human Genome Study (below) is helping to answer that challenge. (Remember the magnitude of these genetic variants when we talk about cancer mutations in Chapter 6. It will highlight the concept of “cancering” that we'll be discussing.)

6. The Human Genome Project [14]

As we described previously, the human genome is a complete set of nucleic acid sequences for humans, encoded as DNA within the 23 chromosome pairs in cell nuclei. The HGP was one of the greatest feats of scientific exploration in history. Beginning on October 1, 1990 and completed in April 2003, the HGP gave us the ability, for the first time, to read nature's complete genetic blueprint for building a human being. Since the completion of the HGP in 2003 and the continuing advances in AI, the scientific community now has the tools (e.g., NGS) to locate and identify genetic mutations in timeframes of minutes, hours, and days, versus the original “non-AI processes” of weeks, months, and years, if at all. This capability was the singularly responsible technology that allowed researchers to develop a COVID-19 vaccine in less than a year (vs. the multiple years and decades needed in the past) and then rapidly identify viral variants as they developed.

This astronomical advance in genetics has changed the current face of immunology and health care. It provides a future for continuing, expanding diagnostic capabilities (locating and identifying mutations), and treatment options (engineering and manipulating gene mutations [CRISPR-Cas9, CAR-T, etc.] to reduce their negative effects, to be discussed in Section 2). Finally, the HGP has introduced a new level of real personalized, “precision medicine” and prevention by enabling the correction of gene abnormalities in many cases before they produce their negative effects.

7. Precision (personalized) medicine and prevention [15]

The concept of precision medicine (*aka* personalized medicine) has become a significant part of human genetics. While it is indirectly related to immunology, its potential value in health care is enormous with profound applications and impact on the future of care including the diagnosis, treatment, and potential cure and prevention of all the immunological diseases.

It is a concept that uses genetics as its foundation. According to the CDC's (Center for Disease Control) “Precision Medicine Initiative,” this relatively new term takes into account individual variability in genes, environment, and lifestyle for each person. It allows doctors and researchers to predict more accurately which treatment and prevention

strategies for a particular disease works in which groups of people versus the “one-size-fits-all approach.” Its goal is to find unique disease risks and treatments that work best for patients. It includes

- the use of family history, screening for diseases before you get sick;
- tailoring prevention;
- tailoring treatments;
- looking at the patient's DNA.

7.1. “All of Us”

As part of Precision Medicine, an initiative by the National Institute of Health (NIH) entitled “All of Us” [16] will track history and physical findings, genetics, behavioral, and environmental factors of one million Americans for several years to assess health factors; develop healthcare solutions that make the best decisions to prevent or treat disease; predict epidemics; and improve the quality of life. This concept combines medicine, biology, genetics, statistics, and AI computing to create large-scale biobanks of complete genome-sequenced and phenotype information from hundreds of thousands of people.

Researchers are already taking the first steps toward developing personalized treatments for diseases. They are applying AI and machine learning to multiple data sources, including genetic data, electronic health records, sensor data, environmental, and lifestyle data. Meanwhile, sustained collaboration across disciplines and institutions in this unique precision medicine effort is proving to be the most promising research in the healthcare field. Large corporations, universities, and government-funded research collectives are developing precision treatments for complex diseases including autoimmune diseases and cancers. In the coming years, precision medicine will be part of routine health care.

8. XCI (lyonization)

This section on genetics brings us back to the embryology discussion we started in Chapter 1 regarding X chromosome inactivation (XCI) or “lyonization” to “equalize” the influence of the X chromosome between males and females (a quick one paragraph refresher on page 5 might be worthwhile). XCI only happens in females and affects almost all of the 900 to 1400 genes on the X chromosome. Cells can express X chromosome genes differently (and randomly) from each other. This is called cellular mosaicism and it gives females more diversity than males (remember, after XCI, the female has more X chromosomes than the male), meaning that females have more genetic options during development and thus, more ways to prevent disease [17].

Many genes can undergo changes, called mutations, which, in some

cases, can make a person more likely to get certain diseases. Diseases caused by mutations in genes on the X chromosome are called X-linked diseases, that is, genetic diseases in which the disease-causing gene exists on the X chromosome. Males do not experience XCI because they only have one X chromosome. So, if males have a disease-causing gene on their X chromosome, it will be active and more likely to cause disease. Conversely, XCI helps protect females from X-linked diseases but, given the combinations and permutations created by 900–1400 X chromosome genes, cellular mosaicism does not exclude their possibility, though rare (e.g., Rett disease, Turner syndrome).

Assume a woman has a healthy copy of a gene on one of her X chromosomes and a mutant copy of the same gene on her other X chromosome. If the X chromosome with the mutant copy is turned off due to XCI "silencing," the X chromosome with the healthy copy will stay active and express normal gene traits. If a female inherits a gene responsible for an X-linked disease and has one copy that's abnormal and one copy that's normal, the abnormal gene is almost always the one that's turned off. The normal gene, for reasons yet unknown, almost always is allowed to stay on, thus providing greater protection against certain diseases in the female. In males, of course, X-linked diseases (e.g., hemophilia, Duchenne muscular dystrophy, etc.) manifest because they only have one X chromosome, and so those mutated genes have to show up. So, in the X-linked diseases, the XCI seems to protect the female [18]. That, however, is not the case for females regarding autoimmune diseases and cancers (i.e., more X chromosomes mean more mutations) as we will explain in Chapters 5 and 6.

Yet another compelling factor beyond the female sex hormones and X chromosome genes predisposing females to autoimmune disease is the microbiome. This fascinating entity is included in this chapter on genetics and genomics because of its functions as "the second genome" with its own subset of immune reactive cells. Let's introduce the microbiome here to establish your understanding of its intricate genetic and immunologic interconnections. But we'll postpone the discussion of its relationship to autoimmune disease until the microbiome section later in Chapter 6.

9. The "microbiome"

Just as I debated (with myself) at the beginning of this chapter about where I should position it in the book, I have had the same uncertainty about where I should place the subject of "the microbiome" because of its diversity. I'm putting it here, along with the immunogenomic discussion, because the microbiome is sometimes referred to as "the second genome of the human body." Now let's see if we can make some sense of that scientific idiom.

We'll start with the interesting and probably little-known fact that there are more bacteria in our body (greater than 30 trillion) than there are human cells with an estimate of approximately 57% bacteria (actually a

mixture of microbes) to 43% human cells. In other words, we're more microbe than we are human! Surprising? It was to me when I first learned this arcane fact. But this interesting piece of molecular (and micro) biology has resulted in giving this enormous array of microbiota (microorganisms found in a particular habitat, in this case, our body) the pseudonym, “the second genome of the human body.”

The unique difference in the human versus the microbial genome is their evolutionary development. Whereas the DNA of the human genome is very stable allowing for predictable heredity with only slight mutations over time (sometimes over millions of years), the microbial genome (“the second genome”) changes far more frequently. As a matter of fact, the only time it is predictable is at birth. That is when the newborn will inherit some microbes from mother. This is a critical process that allows the baby to begin to deal with pathogens outside of the womb. The transfer of microbes to the newborn happens during vaginal births when the baby is exposed to mother's gut and vaginal microbes during delivery. This triggers the baby's immune system, allowing for early protection and more so, better ability to absorb nutrients from mother's breast milk. The process does not occur in Caesarean section births and is one theory as to weaker immune systems in babies from Caesarean section.

All human body surfaces and all cavities that communicate with the exterior are inhabited by complex, individualized, and variable ecosystems of microorganisms (bacteria, viruses, protozoa, fungi, and even primitive archaea) whose composition is influenced by host genetics. Everything in this world is covered by microbes, so obviously we are constantly inhaling and ingesting microbes and creating our own gut-microbiota. And so, the theory is that the constant 24/7 exposure of gut microbes to immune cells, from birth on, creates a chronic (albeit subclinical most of the time) inflammatory condition in our gastrointestinal (GI or gut) system from oral (e.g., periodontitis) to colorectal (e.g., inflammatory bowel) syndromes. This chronic state produces a “symbiosis,” in fact, a “biological synergy” between immune cells and the microbes [19].

This biological synergy includes fighting off invading microorganisms like pathogens, thanks to the antibody-encoding gene of our human genome (from Chapter 1, the discovery that won Susumu Tonegawa the 1987 Nobel Prize). Our immune system has an almost infinite array of antibodies to achieve this goal. But, because of the enormity of the task including digestion, nutrition, manufacturing vitamins, converting nutrients to energy and proteins, controlling obesity, even managing anxiety, and mood (using hormones and neurotransmitters to the brain), we enlist help from “the second genome,” the “normal flora” microbes or, “the microbiome.” No doubt, imbalance of this powerful microbiome can produce serious health consequences, while proper balance (diet, exercise, weight control, etc.) can be a major factor in health and wellness.

The microbiome also involves yet another specialized subset of the T cells and a rather powerful one at that. Discussed previously in Chapter 1, it is the T regulatory cell (or T_{reg}, also referred to as the T suppressor or

T_S cell). One of its functions is to suppress the immune system when it becomes too overactive and dysregulates. It has been shown that bacteria from the microbiome trigger T_{reg} cells (and other killer immune cells like natural killer cells [NKs] and T cytotoxic [T_C] cells). Take a quick look at Fig. 1.6 showing how these Immune cells proliferate during innate immunity. You can see that this function becomes a mitigating force against inflammation, autoimmune disease, even cancers as it modulates the immune system (more in this microbiome–disease association in their subsequent, respective chapters).

This microbiome–disease association presents an interesting theory about human's inherent desire and continuing effort to "clean" everything (antiseptics, antimicrobials, organic foods, etc.), sometimes called the "hygiene hypothesis." This human trait may be compromising our microbiome. (Could this be a cause of increasing autoimmune diseases and some cancers?) Microbes ain't going away, so we really should start thinking about how we can better share the planet with them. The answers will lie in supporting the science and immunology of the microbiome, effective public health initiatives, and a better understanding of how-best to harness the microbiome's potential benefits. Studies have demonstrated that probiotics that help balance the microbiome may help improve the immune system. The results, however, of many probiotic clinical trials are still equivocal, especially in treatment of cancers [20].

Regarding cancers and the microbiome, distinct aspects of the microbiota have been reported to have either pro- or antitumor effects. The functional role of the microbiota in regulating systemic immune responses has led to investigations into the impact on cancer immunotherapies, particularly with agents targeting the immunologic checkpoints PD-1 and CTLA-4 (more in Chapter 6). Clinical trials pursuing microbiome-based therapeutic interventions are being conducted with the hope of expanding immunotherapy efficacy. A better understanding of the role of the microbiota on tumor development could lead to the early identification of individuals with high risk for developing cancer. Modulating the microbiome in these individuals could also have implications in cancer prevention [21].

Now, let's continue our discussion about the female bias for autoimmune diseases that we started in Chapter 1 with the XCI discussion, revisited it in this chapter already and now again, this time looking at its role with the microbiome. Microbiome aberrations have been observed in the vast majority of immune-mediated diseases. The gut microbiota plays a critical role in maturation and modulation of innate (mentioned above) and adaptive immunity [22]. Both the gut immune system and human microbiota exhibit sexual dimorphism, that is where immune tissues in the gut of the male show greater innate and adaptive immunity than that of the female. The aggregate science-based data definitively demonstrate that sex and androgens regulate the composition and function of the microbiome as a direct instigator and a definitive sex bias toward females

for autoimmune disease [23].

MicroRNA (miRNA) is a noncoding RNA gene abundant on the female X chromosome and essential in gene expression (more on microRNA in Chapters 5 and 6). The X chromosome contains 10% of all miRNAs detected in the human genome [24]. This gene is also endogenous in the gut intestine and exogenous from diets. It is believed to play an influential role in microbial colonization and intestinal immunity by modulating intestinal immune responses and gut microbiota. Fecal miRNAs are potential biomarkers for intestinal diseases, such as colorectal cancer and inflammatory bowel disease (IBD). The relationship between microRNAs, gut intestinal microbiota, and host immunity is decisive for the homeostasis or dysbiosis (an imbalance between the types of organism) of the gastrointestinal environment. The growing belief is that aberrant expression of these microRNAs leads to immunological abnormality and autoimmune diseases [25].

I do hope you were able to follow this fascinating and compelling aspect of XCI, immunogenomics, and the microbiome. It's new and evolving science will definitely help us better understand the paradox of autoimmunity.

10. Epigenetics [26]

Chemical compounds added to a single gene can regulate the gene's activity. Such modifications are known as epigenetic changes [27]. The epigenome comprises all chemical compounds and molecules that have been added to the entirety of one's DNA (genome) to regulate the activity (expression) of all the genes within the genome. The chemical compounds of the epigenome are not part of the DNA sequence. They exist on or attached to DNA ("epi-" means above in Greek). Epigenetic modifications remain as cells divide and sometimes, they can be inherited through generations. Patterns of epigenetic modification vary among individuals, in different tissues within an individual, and even in different cells [28].

Because errors in the epigenetic process, such as modifying the wrong gene or failing to add a compound to a gene, can lead to abnormal gene activity or inactivity. This can cause genetic disorders. Conditions, including cancers, metabolic diseases, and degenerative disorder have all been found to be related to epigenetic errors. Again, these "errors" will be addressed in Section 2 in the continuing discussion of immunogenetics and immunogenomics.

11. Cytogenetics

Cytogenetics involves the examination of chromosomes to identify structural abnormalities. It's hard to wrap one's head around such testing methodology when we consider the numbers presented in the discussion above. Think about the multiples of "20,000 and 25,000 genes" in

“trillions of cells” in the human body with “3 billion DNA base pairs” in each cell. Exponentially that sum would be 7.5×10^{25} (if my math is correct—not likely beyond 20 zeros). And that would be the genome for one human being. Finding an abnormality (mutation or variant) in that genome is what “big data analytics” (mentioned above and discussed further, below) is all about.

Progress in genetic testing was stalled by the complexity and enormity of the data that needed to be evaluated. Instead, the extensive datasets (e.g., 7.5×10^{25}) in cytogenetics provide training for AI deep learning (convolutional neural networks or CNNs) algorithms resulting in dramatically faster (than human) and more accurate analysis [29]. With such advances in AI and machine learning applications, researchers are now able to interpret data better and faster, and act on genomic data through genome sequencing (as exemplified in the variant viral detections with COVID-19 and vaccine development). Because AI systems can do it faster, cheaper, and more accurately, they gain perspective on the particular genetic blueprint that orchestrates all activities of that organism. These insights are helping health professionals make better decisions about care (e.g., precision medicine [30]), what an organism might be susceptible to in the future, what mutations might cause different diseases, and how to prepare for the changes [31]. This is an extraordinary advancement in precision medicine and more so, preventive medicine, the holy grail of healthcare.

12. Big data analytics in genetics and genomics [32]

“Big data” is an evolving term that describes a large volume of structured (databases), semistructured (structured data without fixed limits), and unstructured (e-mail messages, word processing documents, videos, photos, audio files, written notes) and clinical observations (called heuristics) data that have the potential to be mined for valuable information. For any data to be useful, it must be analyzed, interpreted, and then addressed. AI algorithms are capable of analyzing enormous amounts of data in almost instantaneous speeds whose volume or complexity would previously have made analyzing them unimaginable. Big data analytics' use in genetics and genomics may arguably be AI's most profound contribution to immunology and the future of healthcare.

A person's genes are what “predispose” them to dysregulation of the immune system, which in turn yields chronic inflammation and, in effect, creates the pathological damage to cells, tissues, and organ systems synonymous with all diseases (another “follow the bouncing ball” effect. Sorry about that.). As we discussed, the environmental factors (e.g., smoking, pollution) along with the inherited alleles that an individual possesses for a specific gene (the genotype) combine to produce the “phenotype trigger” and the clinical manifestations of the disease state.

This recipe for disease is also responsible for immune and autoimmune diseases, for congenital and acquired genetic disorders, for cancers, and in fact, for just about all the conditions being discussed in this book. Thus, throughout our discussions of specific disease entities, you will recognize common denominators in their diagnosis and treatments (as will be mentioned in the discussion on “nonspecific” drug therapies in autoimmune disease) [33]. What will change for each disease are the clinical manifestations (phenotypes) of the individual disease categories based on cellular, tissue, and organ system(s) involved [34].

13. Brief research summaries on genetics and genomics

(Reference citations for each research study presented below are provided at the end of each study. Also, a listing of available scientific reference sources and databases used by the author are included in the book's Acknowledgments).

1. Advancement and progress in genetic and genomic research has created breakthroughs and new capabilities in medicine and immunology never imagined just five to 10 years ago. It has evolved from seeking to understand the fundamentals of the human genetic code to examining the ways in which the code varies among people and then utilizing that knowledge to introduce interventions targeting the underlying causes of disease. Since the completion of the first full mapping of the human genome in 2003, attention has graduated from searching for genes to discovering their functions. Systematic genetic mapping in families and populations now helps scientists pinpoint the genetic variants that contribute to human disease [35].
2. The discovery of genes responsible for more than 5000 Mendelian disorders (single-gene disorders like Downs' syndrome, cystic fibrosis, Duchenne muscular dystrophy, etc.) has facilitated genetic diagnostics for many patients, pregnancy-related counseling, new drug treatments, and gene therapies. The discovery of more than 100,000 associations between genomic regions and autoimmune diseases has uncovered new related biologic mechanisms. Risk factors for IBD, heart disease, breast cancer, and other conditions are being identified, while studies of cancer genomes have revealed hundreds of genes in which somatic mutations initiate and propel tumor growth. All of these discoveries are providing information that advance the development of new drugs [36].
3. Genomics research is moving beyond just analyzing DNA variations. Through new methods for single-cell RNA sequencing

and chromatin analysis, researchers are now studying patterns of gene expression in individual cells. Tens of millions of cells have been characterized thus far with the goal of developing a complete cell atlas of the human body. This effort is revealing hundreds of new cell types including immune system cells and characterizing the ways in which these cell types differ between healthy people and people with various diseases including the autoimmune diseases [37].

4. Genomic-technology advances like CRISPR-Cas9 (see Chapter 5, page 137) will continue to move basic science forward in powerful ways, some not yet envisioned. Understanding of human genetic variations and their biologic consequences will also advance. Increasing abilities to target genetic mutations in vivo with oligonucleotides or gene editing should put many Mendelian disorders within reach of therapies—and maybe cures. But uncertainties remain and not all the big questions can be answered by science alone. How do we balance scientific progress with emerging ethical issues regarding the use of genome-editing technologies? How do we protect the bioethics, privacy, and cultural standards at potential risk? These questions need to be addressed regarding the science of genetics and genomics, as well as immunogenetics and immunogenomics, progress [38].

5. Unraveling the genetic and environmental underpinnings of autoimmune disease has become a major focus at the National Institute of Environmental Health Sciences of the NIH [39]. The process of identifying the offending genetic sites (likely multiple mutations) in an individual's genome is overwhelming [40]. As you will recall, the potential for those mutations in the sequencing of the four base compounds within the 20,000 to 25,000 genes in the human genome exceeds 2.53×10^{20} possibilities spread among the 37.2 trillion somatic cells. Thanks to AI, more specifically, big data analytics and deep learning (convolutional neural networking—CNN), genetic loci for immune disorders (immunodeficiencies, autoimmune diseases) are now being identified in a timely diagnostic manner (days to weeks vs. months to years). This application of AI to better identify genetic mutations and their associated disease states, combined with the now FDA approved cellular and gene therapies presented above, has created new horizons in the treatments, management, cures, and prevention of disease [41].
6. Predictive and presymptomatic testing is used to detect gene mutations associated with disorders that appear after birth, often later in life. These tests can be helpful to people who have a family member with a genetic disorder, but who have no features of the disorder themselves at the time of testing.

Predictive analytics testing can identify mutations that increase a person's risk of developing disorders with a genetic basis, such as certain types of cancer. The results of predictive and presymptomatic testing can provide information about a person's risk of developing a specific disorder and help with making decisions about medical care (see Cancers, Chapter 6). Predictive genetic testing is becoming increasingly available to the general public, but is not yet regulated or closely monitored by the CDC or NIH [42]. Buyer beware.

Chapter highlights on genetics and genomics

1. Genetics can be considered the most distinct and essential feature of our immune system, particularly in its positive and "friendly" innate immune form and function.
2. Immunogenetics is the branch of science that explores the relationship between the immune system, genetics, and mutations (genetic variant, the underlying cause of all abnormalities), while immunogenomics is the study of the total human genome or the complete set of genetic instruction's influences on immunity.
3. Every person has about 20,000 to 25,000 genes with two copies of each gene (diploid pairs), one inherited from each parent.
4. Alleles are forms of the same gene with slight differences in their sequence of DNA base compounds that contribute to a person's unique physical features (their phenotype).
5. Genetics or molecular biology includes the cell, its nucleus, chromosomes within the nucleus, the DNA strands within the chromosomes, and the base compounds (nucleotides) of the genes within the chromosomes.
6. The "central dogma of molecular biology" (or "transcriptomics") includes transcription and translation. In transcription, information stored in a DNA's gene sequence is copied to a smaller, single-stranded ribonucleic acid molecule called mRNA (messenger RNA). Then the mRNA molecule transfers the information (the DNA "code message") from the nucleus into the cell cytoplasm.
7. In translation, mRNA interacts with a specialized complex in the cytoplasm called a ribosome that reads the transcribed DNA code and translates the gene sequence into genetically programmed polypeptide chains that bind together to form amino acids and, in a process called protein synthesis, the mRNA attaches to a ribosome while another type of RNA called transfer RNA (tRNA) binds the amino acids together in chains to form functional three-dimensional body proteins (tissues,

organs, cells, enzymes …you name it).

8. All the cellular proteins of the immune system (T and B lymphocytes, their surface receptors like HLA, CD proteins, TLRs) are all genetically produced and encoded (programmed) from the major histocompatibility complex (MHC) genes referred to as “the keys to selfrecognition.”
9. Immunogenomics reads the genetic code of a person through DNA sequencing and studies the interactions of genes with each other and with a person’s environment (“precision medicine”).
10. Work in X chromosome inactivation (in women), the microbiome (“the second genome”), epigenetics (gene modification), and cytogenetics (structural gene abnormalities) are being advanced through the application of AI’s big data analytics in genetics and genomics.

References

1. King's College London. Genetics play a significant role in immunity. *ScienceDaily* . January 5, 2017.
2. Genetics Home Reference (GHR). *What is a gene? U.S* . Library of Congress; July 16, 2019.
3. Biancotto A, McCoy J.P. Studying the human immunome: the complexity of comprehensive leukocyte immunophenotyping. *Curr Top Microbiol Immunol* . 2014;377:23–60.
4. “The definition of genetics”. Retrieved 25 October 2018. www.dictionary.com.
5. *Transcriptomics* . Nature.com; September 29, 2019.
6. *What are proteomes?* Uniprot Consortium; January 22, 2020. .
7. Genetics Home Reference. *What is a genome?* U.S. National Library of Medicine. USA.gov; September 10, 2019.
8. Khan Academy, . *DNA sequencing. Creative commons* . Rice University; 2019.
9. Lindor M.N, Thibodeau S.N, Burke W. Whole-genome sequencing in healthy people. *Mayo Clin Proc* . 2017;92:159–172. doi: 10.1016/j.mayocp.2016.10.019.
10. Wetterstrand K.A. *The cost of sequencing a human genome* . National Human Genome Research Institute. NIH. USA.gov; July 10, 2019.
11. Genetics Home Reference. *What is a gene mutation, and how do mutations occur? NIH* . National U.S. Library of Medicine. USA.gov; October 15, 2019.
12. Zhang S. *Your body acquires trillions of new mutations every day, and it's somehow fine?* The Atlantic; May 7, 2018.
13. Scally A. The mutation rate in human evolution and demographic inference. *Curr Opin Genet Dev* . December

2016;41:36–43.
14. National Institute of Health. *The human genome project* . National Human Genome Research Institute; 2019.
15. Genetics Home Reference. *What is the precision medicine initiative?* NIH. National U.S. Library of Medicine. USA.gov; 2019.
16. National Institute of Health (NIH). *The future of health begins with you. All of Us and Precision Medicine Initiative* . U.S. Department of Health and Human Services (HHS); 2020.
17. Migeon B. *Females are mosaics: X inactivation and sex differences in disease* . Oxford, UK: Oxford University Press; 2006.
18. Austin C.P. *Lyonization* . National Human Genome Research Institute; April 4, 2014.
19. Zitvogel L, Ayyoub M, Routy B, Kroemer G. Microbiome and anticancer immunosurveillance. *Cell* . April 7, 2016;165(A):276–287.
20. Lu K, Dong S, Wu X, Jin R, Chen H. Probiotics in cancer. *Front. Oncol.* 2021;11:638148.
21. Matson V, Chervin C.S, Gajewski T.F. Cancer and the microbiome-influence of the commensal microbiota on cancer, immune responses, and immunotherapy. *Gastroenterology* . 2021;160(A):600–613.
22. Pickard J.M, Zeng M.Y, Caruso R, Núñez G. Gut microbiota: role in pathogen colonization, immune responses, and inflammatory disease. *Immunol Rev* . September 2017;279(1):70–89.
23. De Luca F, Shoenfeld Y. The microbiome in autoimmune diseases. *Clin Exp Immunol* . 2019;195(1):74–85. doi: 10.1111/cei.13158.
24. Plotnikova O, Baranova A, Skoblov M. Comprehensive analysis of human microRNA–mRNA interactome. *Front Genet* . 2019;10:933.
25. Bi K, Zhang X, Chen W, Diao H. MicroRNAs regulate intestinal immunity and gut microbiota for gastrointestinal health: a comprehensive review. *Genes* . 2020;11(9):1075.
26. Genetics Home Reference (GHR). *What is epigenetics?* U.S. Library of Congress; August 6, 2019.
27. Center for Genetics and Society. *Human genetic modification* . 2019.
28. Epigenetics Simplified. *A super brief and basic explanation of epigenetics for total beginners. What is epigenetics* . July 30, 2018.
29. Medline Plus, . *Genetic testing* . NIH. National Library of Medicine; April 25, 2019.

30. Campbell M. Genotype vs. phenotype: examples and definitions. *Genomic Res.* April 18, 2019.
31. Stanford at the Tech Museum Understanding Genetics. Mutations and disease. *Stanford at the Tech* . 2019.
32. He K.Y, Ge D, Hemm. Big data analytics for genomic medicine. *Int J Mol Sci* . February 15, 2017. .
33. Genetics Home Reference. *What is the precision medicine initiative?* NIH. National U.S. Library of Medicine. USA.gov; October 15, 2019.
34. Genetics Home Reference. NIH, National U.S. Library of Medicine. USA.gov. Campbell, October 15, 2019. p. 32.
35. The Human Genome Project. *National human genome Research Institute* . January 9, 2019.
36. Wei H, Lai A, Tan E.S, et al. Genetic landscape of congenital disorders in patients from Southeast Asia: results from sequencing using a gene panel for Mendelian phenotypes. *Arch. Dis. Childhood* . 2021;106:38–43.
37. ChenLiu Y.L, BingLiu, et al. T cell development: old tales retold by single-cell RNA sequencing. *Trends Immunol* . February 2021;42(2):165–175.
38. Fellner A, Ruhrman-Shahar N, Orenstein N, et al. The role of phenotype-based search approaches using public online databases in diagnostics of Mendelian disorders. *Genet Med* . 2021 doi: 10.1038/s41436-020-01085-7.
39. National Institute of Environmental Health Science. *Autoimmune disease* . NIH. USA.gov; 2019.
40. Ramos P.S, Shedlock A.M, Langefeld C.D. Genetics of autoimmune diseases: insights from population genetics. *J Hum Genet* . 2015;60(11):657–664.
41. Noorbakhsh-Sabet N, Zand R, Zhang Y, et al. Artificial intelligence transforms the future of healthcare. *Am J Med* . 2019;132(7):795–801.
42. *What are the types of genetic tests?* U.S. Department of Health and Human Services National Institutes of Health; September 22, 2020.

Section 2

The enemy within us

Outline

Introduction

4. Chronic inflammation: “Enemy #1”

5. Autoimmune disease: when self becomes the villain

6. Cancer: immunology's cruelest enemy and greatest challenge

7. Immunology: The science of pandemics, infectious disease and COVID-19

Section 2 The enemy within us

1. Introduction

You've completed Section 1 and you're probably saying to yourself, “This immunology stuff is a bit heavy, but *fair dinkum* (*aka* “good stuff” [a little shout out to my Aussie mates]). And indeed it is. So, what's with all those innuendos introduced in Section 1? Things like, “the paradox,” “the enemy,” “…a friend to a degree,” words like “dichotomous, villain, cryptic,” or that dumb “…Dr. Jekyll and Mr. Hyde” metaphor?” Between the innate and adaptive immune systems working overtime to defend us, vaccines to protect us, and our own genes constantly building and rebuilding immune system molecules and proteins to keep us healthy and safe, how can our immune system possibly be an “enemy” or a paradox?

Having paid a peaceful, relatively untroubled visit to “our friend,” the regulated immune system (in Section 1), now it's time to visit the darker, far less pleasant side of immunity, the “dysregulated” immune system. We visited it briefly in Section 1, but we have yet to scratch the surface of the dysregulated side of immunology. This is the side where the system, in its otherwise supportive efforts, “paradoxically” begin to produce less-than-positive pathophysiologic (disease) and clinical problems. Ignoring this troublesome side of the immune system would be tantamount to an incomplete, frankly inaccurate and irresponsible portrayal of this vital human system. In fact, given the harmful nature of the dysregulated immune system, the negative side of immunity can arguably be considered the more serious and consequential information and conversation about this otherwise supportive system. Sorry for disappointing you after singing the praises of the immune system in Section 1. But, I'm afraid “we're not in Kansas anymore, Toto.”

So, notwithstanding the accolades and ingratiating Section 1 discussion about the value of the immune system and its vigilance in defending us, its synergies with our genes, and its protective immunization features, it's time to reveal its cryptic nature, its darker side, the dangers of its dysregulation, and indeed, “the paradox of the immune system” in health, wellness, and disease. These must be addressed in the context of a total

examination of so vital, powerful, and fundamental a system of the human body that enigmatically and simultaneously protects us while posing an existential threat to our health and wellbeing. It is truly “our best friend and our worst enemy” and thus, as confusing (and paradoxical) as that might sound, it becomes the compelling reason for us to understand the dark side of “this enemy within us.” And so, to stretch the “Oz” metaphor just a bit further (probably stretched too far already), it's time to “look behind the curtain.”

4: Chronic inflammation

"Enemy #1"

Abstract

The role and function of the immune system is to defend the human organism from foreign (antigenic) invasion and resultant disease. When the innate immune response ("our best friend") is overwhelmed for multiple reasons by a pathogenic source (substance or stress), adaptive immunity initiates acute inflammation and hypersensitivity reactions to arrest the dysregulated condition. If unsuccessful, a separate and distinct form of inflammation, chronic inflammation develops as its devastating successor (our "worst enemy" and "a paradox of the immune system"). Adaptive immunity then induces an array of destructive cellular and chemical proinflammatory cytokines, chemokines, pathogenesis, immunohistopathologic, and pharmacodynamic processes. All of these biologic activities insidiously devolve into *all* (emphasis on *all*) human diseases, making chronic inflammation the progenitor of *all* human disease (a unique hypothesis proposed and defended in this chapter). The chapter includes diagnostic considerations in chronic inflammation and introduces immunomodulating therapies and presents chronic inflammation's inextricable role in autoimmune and all other categories of human disease.

Keywords

Biologics; Hypersensitivity; Hypothesis; Immunohistopathologic; Monoclonal antibodies; Paradox; Pathogenesis; Pharmacodynamic; Pro-inflammatory cytokines

> *Out of suffering have emerged the strongest souls; the most massive characters are seared with scars.*
>
> *Kahlil Gibran*

1. Introduction

Think for a moment of the words you have heard most frequently mentioned when listening to news about COVID-19. Certainly, besides masks and vaccines, among your top choices would likely include "infection" and "inflammation." The reason is simple. The COVID-19

pandemic was caused by an “infectious” agent (i.e., SARS-CoV-2 or the novel coronavirus), but the adverse clinical effects of that infection, “the disease” if you will, are a product of “inflammation,” chronic inflammation to be exact. Whereas acute inflammation produces localized effects, ones that are usually manageable (per our Chapters 1 and 2 discussion), chronic inflammation is a diffuse process, one affecting any (and oftentimes, all) biological tissue(s) or organ system(s) in the body. Generally, it's safe to say, chronic inflammation is difficult to treat, indeed, impossible to treat without removal of the cause, *when and if possible*.

It's inaccurate to single out one infection, or in fact any one pathological etiology, intrinsic (i.e., inherited, metabolic, hormonal, neoplastic, immunologic) or extrinsic (i.e., infectious, toxic, traumatic) that can produce disease in the human organism to qualify it singularly as chronic inflammation. Rather, as I proposed in the Preface of this book, it is my hypothesis that the basis of *all* diseases (emphasis on *all*) is chronic inflammation. I recognize the magnitude of that statement (the qualification “*all”* not being typically used in healthcare) and I will take my best shot in this Section (2), using autoimmune diseases, cancers, and infectious pandemics to defend the theory.

Whereas most of the intrinsic and extrinsic etiologies mentioned above convert through secondary physiologic, histologic, pharmacologic, pathological pathways into chronic inflammation, autoimmune diseases, and cancers use “primary genetic mechanics” (mutations, genotype, epigenetics, etc.) as their direct route to chronic inflammation. But whatever the pathway, secondary pathology or primary genetics, after all is said and done, the basis of *all* human disease is chronic inflammation. As stated in a definitive, comprehensive 2018 article in Frontiers in Medicine (“Inflammation-Nature's Way to Efficiently Respond to All Types of Challenges: Implications for Understanding and Managing “the Epidemic” of Chronic Disease), “… excessive inflammation is a common thread in all forms of disease development and progression [1].” I'll spend much of this Section 2 trying to make a case for that hypothesis.

2. Causes (etiologies) of chronic inflammation [2]

As we emphasized in Chapters 1 and 2, the only effective way to cure a disease caused by an antigen is to identify (i.e., diagnose) and remove the antigen. In most cases, the innate or adaptive immune responses are, by and large themselves successful in eliminating antigens (selfresolution) and ergo, the dysregulated state regresses toward normal. Such regression will also aid in the reduction in the active immune process with or without residual tissue or organ damage depending on the intensity and duration of the persistent inflammatory state. Short of antigen removal and resolution of the disease process, one of five possibilities is likely to cause persistent (chronic) inflammation (Table 4.1).

(1) The diagnosis was incorrect and the antigen (substance or stress) was, in fact, not removed.
(2) There is an abnormality (a congenital or acquired mutation) in the patient's genome making them susceptible to dysregulation of their immune system.
(3) There is chronic exposure to environmental factors (e.g., toxins, pollution, smoking, microbiota [the microbiome], etc.) that serve as a recurring stimulus to inflammation.
(4) Accumulating inflammatory byproducts of cellular and humoral (chemical) components (proinflammatory cytokines) result in a persistent inflammatory and neural stimuli.
(5) Finally, the causative antigen may be:

- (a) an inherent disruption to homeostasis (e.g., environmental factors, stress);
- (b) an innate, unknown autoantigenic factor; or
- (c) "rogue B cells" and epitope spreading.

While all five possible causes (above), direct or indirect for chronic inflammation, in the case of item #5's three factors, the disease process can be considered an autoimmune disorder. So, effectively, chronic inflammation (Enemy #1) can be considered the principal etiology (cause) of autoimmune diseases (to be discussed fully in Chapter 5, when "self" (autoantigens) becomes Enemy #2 or "our second worst enemy."

Table 4.1

1. First, the diagnosis was incorrect and the antigen (substance or stress) was, in fact, not removed. 2. Second, there is an abnormality (a congenital or acquired mutation) in the patient's genome making them susceptible to dysregulation of their immune system. 3. Third, there is chronic exposure to environmental factors (e.g., toxins, pollution, smoking, etc.) that serve as a recurring stimulus to inflammation. 4. Fourth, accumulating inflammatory byproducts of cellular and humoral (chemical) components (proinflammatory cytokines) result in a persistent inflammatory stimulus. 5 An abnormal immune response to "self": a. Disruption of homeostasis (*Yin Yang*); b. Innate autoantigens from inflammatory process; c. *"Rogue B cells"* and epitope spreading.

Theories on etiologies and pathogenesis of chronic inflammation.

Source: Foundations of AI in Healthcare and Bioscience; Catania; Academy

Press. November 2020.

In fact, the five etiologies (causes) and the pathogenesis (disease process) of chronic inflammation are intimately related to autoimmune diseases. As such, we'll hold off on an in-depth discussion of the five causes of chronic inflammation until Chapter 5. Rather, let's first try to better understand what chronic inflammation actually is (a lot to unpack here), in fact, the basis of autoimmunity, and the overt and covert etiology of *all* autoimmune diseases. Once you understand chronic inflammation, you will, de facto, understand autoimmunity and autoimmune disease. You'll see what I mean as you read these next two chapters.

3. Advancing adaptive immunity (from acute to chronic inflammation)

Back in Chapter 2, we described the classic signs of adaptive immunity's acute inflammatory response (rubor, calor, dolor, tumor, and function laesa) and its therapeutic strategies. We also described the four cellular reactions (hypersensitivity or "overreactions") associated with the adaptive immune response [3]. These are referred to as the Type I to Type IV hypersensitivity reactions described in Chapter 2 and always designated by Roman numerals (for the reason I mentioned as, "Beats me."). They included:

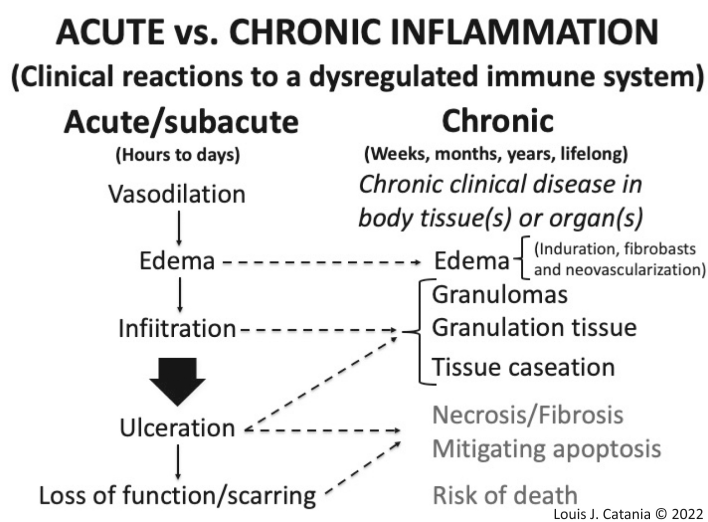
> Type I: The immediate, allergic (or anaphylactic) hypersensitivity response;
>
> Type II: The cytotoxic hypersensitivity reaction;
> Type III: The immune-complex hypersensitivity reaction; and
> Type IV: The cell-mediated, delayed reaction

As we explained, these reactions usually commence during the acute inflammatory stage (back to Figs. 1.6 and 2.1) where they exhibit their more classic clinical signs and symptoms. Then we indicated that their greatest pathophysiological manifestations play their most prominent role in the chronic inflammatory process. In fact, these four hypersensitivity reactions are the segue from acute inflammation to chronic inflammation (remember old Satchel Paige looking over his shoulder?). On the acute side (mostly the left side of Fig. 2.1), these hypersensitivity overreactions initiate the inflammatory cascade that we discussed in some detail back in Chapter 2 (page 31). Now we will present the immunologic conversion from acute inflammation to its chronic form represented by the biochemistry and molecules on the right side of the cascade, plus many more elements of the immune system to be introduced here. So, be forewarned, this is serious stuff from here on.

4. Differences in chronic inflammation from acute inflammation

One can ask at this point in a discussion on immunology, “So, other than duration, what's the difference between acute inflammation and chronic inflammation?” The differences are significant enough to consider chronic inflammation a distinct and separate disease entity from acute inflammation, notwithstanding somewhat similar names. (There really should be a separate and distinct name for chronic inflammation. How about “*pathomelitis*” as a neologism? [Etymology: *patho* = disease; *ome* = complete set of; *(l)itis* = inflammation]. If you agree [after reading this Section], send your cards and letters to the National Institute of Health (NIH) recommending the change. But no demonstrations, rallies or marches, *please!* Meanwhile, to keep this discussion “contemporary,” I'll continue to use “chronic inflammation”…until NIH makes the change official.)

The distinct difference between acute annd chronic inflammation include: (1) a difference in the pathophysiology and histopathology (cells and tissue) between the two; (2) a difference between the pharmacology and pharmacodynamics between the two; and (3) perhaps of greatest consequence, a dramatic difference between the clinical course, beyond duration, of acute versus chronic inflammatory disease. Let's look at each of these differences more closely to demonstrate the uniqueness of chronic versus acute inflammation. Rather than repeat illustrations (in an effort to save trees, and Lord knows we must), let's rely on the relevant graphic resources from Chapter 2 that we need for this following discussion. Those graphics from Chapter 2 include Fig. 2.2 (page 33), 2.3 (page 37) and to a lesser degree, Fig. 2.4 (page 38).



Louis J. Catania © 2022 **Figure 4.1**

Acute versus chronic inflammation.Besides duration, chronic inflammation is

distinguished from acute inflammation by its variable and more invasive pathological and histologic (cellular) comparative counterparts to the acute level.

4.1. Histopathology and pathophysiology of chronic inflammation

First, let's consider the histopathological (cells and tissue) differences between acute and chronic inflammation. As opposed to acute inflammation, chronic inflammation includes unique histopathological tissue changes, not necessarily to the exclusion of the corresponding acute inflammatory histopathology counterparts (Fig. 4.1). In chronic inflammation edema and neovascularization (newly developing, brittle blood vessels) produce swelling and hardening of the tissue (induration). Cell junctures loosen and produce cell and fluid migration through blood vessel walls (diapedesis) allowing inflammatory substances (cells and byproducts) to continue to accumulate (edema and infiltration) in the tissue. A combination of cytokines induces a specialized molecule, the endothelial leukocytic adhesion molecules (ELAM—right side of Fig. 2.3) that stimulates leukocytic (neutrophil) adhesion to the endothelial vessel wall. Then cellular migration associated with surface proteins and chemokines produce blood vessel wall permeability (diapedesis) and extravasation (escape from vessel—Fig. 2.4) of the neutrophils.

Localized accumulation of monocytes, lymphocytes, neutrophils (WBCs), and giant cells (called granulomas) from the inflammatory response convert to fibroblasts producing further tissue induration and fibrinization. These granulomatous changes (areas of inflammation) produce loss of tissue function (functio laesa). Meanwhile, caseation (cheesy textured tissue), necrosis (dying tissue), and apoptosis (programmed cell death) are disrupting and destroying tissue. Associated with all of these cellular dysfunctions are resultant molecular biologic immunogenomic and proteomic disturbances (disruption of the cellular proteome [remember the “central dogma of molecular biology” from Chapter 3, page 51?]), the normal cellular proteins expressed by the human genome and the immunome (remember, the total genes and proteins that make up the immune system?). You can see that the magnitude of these histopathological changes in chronic inflammation are quite unique from acute inflammation (as described in Fig. 4.1) and are far more sinister.

Finally, the clinical course of chronic inflammation distinguishing it from acute inflammation, beyond duration, is the magnitude of its pathological consequences on the body at large. As I referenced in the opening paragraphs of this Chapter, more and more medical experts are beginning to view chronic inflammation as the progenitor or originating cause of *all m*ajor human disease categories [4] (Fig. 4.2). The clinical basis for this thesis lies in the diffuse and destructive nature of the chronic inflammatory process. As opposed to the acute inflammatory reaction,

being a localized tissue process, in chronic inflammation the persistent inflammatory mediators and cellular components can damage tissue locally (e.g., psoriasis, a skin disease), or in specific organ systems (e.g., irritable bowel disorder [IBD], a large colon disease), or throughout the entire body (e.g., systemic lupus erythematosus [SLE], rheumatoid arthritis, diseases affecting multiple tissues and organs).

Perhaps, the most devastating pathophysiological changes in chronic inflammation (which are also part of acute inflammation) are the changes in blood vessel walls (adventitia and endothelium) with associated vasodilation, increase in blood flow, capillary permeability (diapedesis as described above and in Chapter 2), and migration of neutrophils into the effected tissue through the inflamed capillary walls (perivasculitis). The localized, and more so, diffuse nature of these vascular changes are what makes chronic inflammation the foundation of the pathological etiologies that precipitate the resultant disease states.

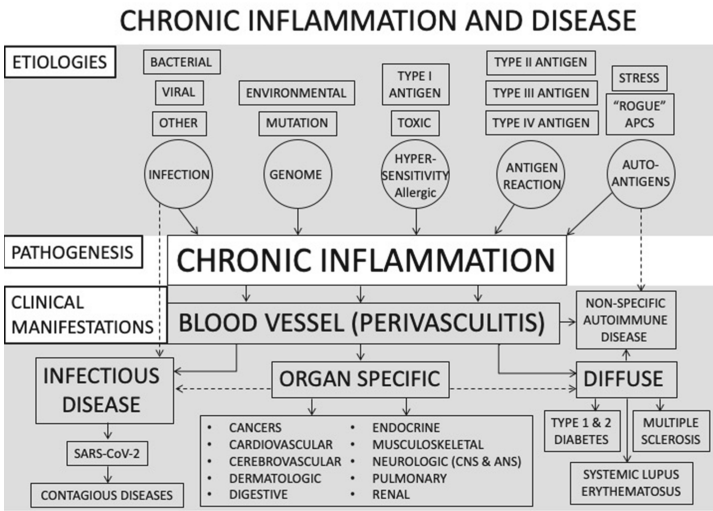


Figure 4.2 Chronic inflammation and disease.Whatever the etiology of chronic inflammation may be, the pathogenesis results in specific organ system-related diseases as well as disseminated disease states including the autoimmune category of disease. Source: Louis J. Catania © 2022.

The infiltration of primary inflammatory cells such as macrophages, lymphocytes, and plasma cells in the tissue site(s), produce inflammatory cytokines, growth factors, and enzymes at a prolonged level. This contributes to the progression of tissue damage secondary ulceration, including granuloma formation, fibrosis (*aka* scarring) and extended tissue (even DNA) damage. These effects compromise the tissue(s) and organ system(s), especially the cardiovascular system (myocarditis), that supply blood vessels throughout the body. As described above, over time, the

tissues and organs, and even the DNA of their cells break down, producing loss of bodily integrity, tissue proteomes, proteomics, and the immunome. These changes manifest themselves as recognizable chronic diseases. And to reemphasize, all of these devastating clinical changes are occurring diffusely in individual body tissues as well as organ systems throughout the body, thus the potential basis for *all* diseases.

4.2. Pharmacodynamics of chronic inflammation

The second difference between acute and chronic inflammation is equally profound clinically. It relates to the pharmacology (cytokines, chemotactic factors, enzymes, hormones, proteoglycans and reactive molecules) of the inflammatory cascade controlled by complex neurogenic and nonneurogenic mechanisms (see the right side of Fig. 2.3). It should be noted here that the drug-related immunotherapies regarding chronic inflammation will be discussed in depth in Chapter 5, where they apply to the autoimmune diseases as well. In fact, as we have stated above, the pathogenesis of all autoimmune diseases discussed in Chapter 5 is the same pathogenesis described here for chronic inflammation. Simply stated, autoimmune diseases are the clinical manifestations of the pathogenesis of chronic inflammation (see the lower half of Fig. 4.2, "Clinical manifestations").

The inflammatory cascade is a complex of pharmacologic agents (cellular and humoral) as well as molecular biologic elements (molecules and leukocytes) interacting to produce immunochemical responses (pharmacodynamics) that drive the immune response. Fig. 2.3 diagram (from Chapter 2) represents only a portion of the elements involved. Table 4.2 is a limited list of pharmacologic, proinflammatory mediators [5] and their actions used to immunomodulate the mechanisms that drive the pharmacodynamics of chronic inflammation. The basis of medical therapies for chronic inflammation (and its associated diseases including the autoimmune diseases) is the immunomodulation (amplifications, supplementation, suppression) of these chemical and molecular components to elicit therapeutic effects (see also Immunotherapies, Chapter 5, page 126 and Table 5.4, page 112).

The immune cells discussed in Chapter 1 and 2 (macrophages, monocytes, etc.) release cytokines such as IL-1, 3, 4 and also tumor necrosis factor (TNF-α), a cytokine protein responsible for a wide range of signaling events within cells that lead to necrosis or apoptosis. Whereas this TNF-α protein is a potent proinflammatory cytokine, it also has been identified as having an important role in the resistance of infection and cancers. This paradoxical multitude of actions presents therapeutic challenges in inhibiting TNF's inflammatory effects while still protecting its beneficial antiinfection and anticancer properties. To wit, you'll notice numerous biologics (see Chapter 5, Table 5.4, page 112) directed at TNF inhibition (e.g., Actemra, Orencia, Humira, Plaquenil, Simponi, Remicade) to allow for alternate drug selections in an effort to maximize

inflammatory inhibition while minimizing suppression of TNF's antiinfectious, anticancer properties (More on TNF in Chapter 5). These therapeutic dilemmas exist in a number of treatment scenarios with chronic inflammation and autoimmune diseases and will be presented as we progress through the clinical discussions.

I must confess to you that this whole pharmacodynamic process continues to get more complex. Read this next paragraph slowly and then go back and reread it. If it still is coming across like a foreign language, put the book down, select your favorite adult beverage and take a 10 to 15min. walk. But please don't quit on me. I'll try my best to make some sense of it for you.

Table 4.2

Inflammatory mediator (label)	# of types	Action
Histamine (H)	10	Vasodilation, smooth muscle contraction, pain, itching
Serotonin (S)	3	Vasodilation, smooth muscle contraction, pain
Bradykinin (B)	3	Vasodilation, smooth muscle contraction, pain
Complement (C)	4	Vasodilation, vasoconstriction, smooth muscle contraction, mast cell degranulation
Leukotriene (LT)	4	Vasodilation, vasoconstriction, smooth muscle contraction, chemotaxis
Prostaglandin (PG)	4	Vasodilation, pain
Fibrinopeptides (F)	1	Vasodilation
Interleukin (IL)	6	Stem cell proliferation, chemotaxis, lysozyme granule release, endothelial cell adhesion, granuloma formation, fever
Tumor necrosis factor (TNF-α)	2	Endothelial cell adhesion, granuloma formation, fever
Colony-stimulating factor (CSF) **Granulocyte (G)** **Granulocyte-macrophage (GM)** **Macrophage (M)**	4	Stem cell proliferation
Platelet-activating factor (PAF)	3	Chemotaxis, lysozyme granule release, platelet aggregation
Tranexamic acid (TXA)	2	Smooth muscle contraction,

		platelet aggregation

Proinflammatory mediators.

Source: Louis J. Catania © 2022.

When the circulating leukocytes (WBCs) that escaped from the blood vessels (diapedesis and extravasation) migrate to the disease site(s), they are activated by various cytokines and chemokines secreted by the macrophages and dendritic cells (APCs). On activation, the leukocytes release additional cytokines and mediators of inflammation. Meanwhile, those neutrophils (WBCs) are also helping to destroy the antigen by phagocytosis through the release of reactive oxygenspecies. Cytokines such as IL-1, IL-6, TNF-α, and T-lymphocytes and B-lymphocytes are an additional line of defense mediating inflammation through several complex mechanisms including secretion of cytokines and production of antibodies and immune complexes (Type III reaction). Circulating platelets also play a role in this pharmacodynamic process by platelet aggregation (adhering to the vessel wall forming thrombus) and mast cell degranulation releasing chemokines and inflammatory mediators [6].

These complex pharmacodynamics in the inflammatory process are being presented here to set the stage for the basis of immunotherapeutic (immunotherapy) use in chronic inflammation as well as all of its associated clinical conditions including the autoimmune diseases, infectious diseases, and cancers. These immunotherapies will be discussed briefly below under “Treatment (Immunotherapies)” and then in greater depth in their clinical applications in Chapter 5's discussion on general and specific therapeutic use in autoimmune diseases.

I hope these last few paragraphs didn't give you a headache. I'll let up on the heavy-duty scientific stuff in the next section. Please forgive me and stick with me.

5. Some (but not all by a long shot) disease categories associated with chronic inflammation [7]

You might be saying to yourself that this chapter on chronic inflammation doesn't make sense. For the past 80 pages, I've been trying to make the point that chronic inflammation is the etiology, the underlying cause, the progenitor (you name it) of *all* diseases. Yet, up to this point, I have named only a few specific disease categories relating to chronic inflammation, specifically the autoimmune diseases and infectious diseases (not that those few categories alone don't cover a pretty good amount of all diseases). But, what about prevalent categories like cardiovascular, cerebrovascular, musculoskeletal, neurologic, and neurodegenerative diseases? Notwithstanding the list of additional categories, yet to be

mentioned, I continue to stand on my hypothesis that " … chronic inflammatory disease is the progenitor or originating cause of *all* the major human disease categories."

A large percentage of the diseases (not necessarily the "disorders"—see the explanation of the distinction between "disorders and disease" in the Preface, page xix) in *all* systemic categories such as dermatology (e.g., dermatitis); pulmonology (e.g., bronchitis), and many "pulmonary disorders" like asthma, COPD, emphysema (but remember, "disorder vs. disease"); ophthalmology (e.g., uveitis, even glaucoma now considered inflammatory [8]); endocrinology (e.g., Type 1 diabetes [see autoimmune diseases, Chapter 5]); gastroenterology (e.g., ulcerative colitis, yet another autoimmune disease), and on and on, all chronic inflammations (look for the "… itis" suffix). So, what I want to do in this section is further confirm my hypothesis by illustrating some (not all) of these major disease categories that are not included in this specific immunologic discussion, but in fact are directly immunologically related to chronic inflammatory-based diseases. Allow me to prove my point.

5.1. Cardio and cerebrovascular diseases

Several landmark clinical studies have been done on the role of chronic inflammation in the incidence of heart attacks and strokes. The findings in the studies show that a sustained low level of inflammation promotes the accumulation of cholesterol or plaques in the coronary and cerebral arteries (atherogenesis). This can trigger an inflammatory response. These plaques are then perceived by the immune system as abnormal and foreign to which they then respond by creating a sort of barrier. Once this happens, loose plaques and blood clots may be the cause of heart attacks and strokes. This can happen to those even with low blood cholesterol levels but who have elevated levels of inflammatory markers in the blood. A recent clinical trial called CANTOS (Canakinumab Anti-Inflammatory Thrombosis Outcomes Study) proved that targeting inflammation without changing cholesterol levels can have a significant impact in reducing the likelihood of heart attacks and strokes by 15%. It also decreased the need for major interventions such as angioplasty and bypass surgery by 30%, proving that addressing inflammation to prevent heart disease is essential [9].

Chronic inflammation, with elevated high C-reactive protein have been identified as risk factors for cardiovascular disease (CVD). Data have shown that inflammation has a central and inciting role in the development of atherosclerosis leading to increased CVD risk. Factors such as endothelial dysfunction, macrophage accumulation, production of tumor necrosis factor (TNF-a), IL-1 and IL-6 associated with the chronic inflammatory process lead to atherogenesis. There is strong evidence that antiinflammatory biologic drugs, such as anti-TNF-α and anti-IL-6 agents, could control atherogenesis and ameliorate CVD risk. New research shows that reduced mortality and morbidity using biologic anti-IL-1b therapy to

treat men and women who have had a prior heart attack provides proof of the pathogenic contribution of inflammation in the development of CVD [10,11].

5.2. Musculoskeletal disease

Muscles and bones are more prone to physical injury and motion "disorders" than to biological pathology. Thus, as mentioned in the Preface of this book, the array of orthopedic abnormalities falls largely into the category of "disorders" versus "diseases." Nonetheless, almost all of us have experienced some sort of physical injury from trauma, repetitive motion, irregular movements, and of course, aging joints during our lives (yeah, tell me about them!). But those aging joints that oftentimes lead to the musculoskeletal "disorders" are in fact inflammatory in origin. Aging is the consequence of the steady, prolonged accumulation of cellular damage related to the failure of clearing necrotic and cellular debris over years. The increasing load of these "damage-associated molecular patterns" leads to the release of proinflammatory cytokines (IL-6 and IL-18) causing ongoing low-grade chronic inflammation [12]. In fact, functional decline of the immune system with aging is referred to as "immunosenescence" and the active inflammatory process as "inflammaging" [13].

Yet, in furtherance of the hypothesis of *all* disease being derived from chronic inflammation, consider the fact that acute inflammation with its associated pain and sometimes functio laesa (loss of function) when not treated (and sometime even when treated) early, will convert into chronic inflammation (e.g., arthritis, bursitis) and the inexorably associated physical (musculoskeletal) "… itis" syndromes. A short list of the more common, often very uncomfortable, and sometimes disabling musculoskeletal orthopedic bone and joint diseases are included alphabetically in Table 4.3. And again, such conditions (excluding congenital and degenerative disorders) are conversions from their primary etiologies (physical injury, etc.) to immunologic pathogenesis and resultant chronic inflammation, including some of very common discomforting, if not disabling bone and joint diseases.

5.3. Neurologic and neurodegenerative disease

The nervous system and the immune system share an intimate relationship wherein they modulate each other through sophisticated "bidirectional crosstalk" (see "Neural downregulation," page 87 below). Contrary to previous beliefs, the brain is not an "immune-privileged" organ. Neurological and neurodegenerative (age or genetically related) brain (central nervous system or CNS) disease shares common hallmarks including cognitive impairment and loss of brain volume following inflammation. Nonneural macrophages can infiltrate the CNS and maintain a separate identity from the brain's glial cells that function as CNS macrophages. This infiltration of nonneural macrophages suppresses the

glial neural functions (impulse transmission) as invading macrophages replace the neural (glial) cells [14]. This opens up the possibility for neural-mediated inflammatory reactions. It also has been identified as the possible cause of the “brain fog” associated with the COVID-19 long hauler's syndrome (see Chapter 7, page 195).

Table 4.3

• Arthritis
• Bursitis
• Elbow pain and problems
• Fibromyalgia
• Foot pain and problems
• Hand pain and problems
• Knee pain and problems
• Lateral epicondylitis (tennis elbow)
• Low back pain
• Medial epicondylitis (Golfer's or baseball elbow)
• Neck pain and problems
• Osteoarthritis
• Osteomyelitis
• Rheumatoid arthritis
• Shoulder pain and problems
• Tendinitis
• Tenosynovitis

Most common chronic inflammatory orthopedic (musculoskeletal) conditions (Alphabetical).

Innate and adaptive immune cells operating in the inflamed CNS may impact neurodegeneration. Genome-wide association studies (GWAs—an approach used in genetics research to associate specific genetic variations with particular diseases) can help to identify gene variants that increase the risk of developing these neurodegenerative inflammatory diseases. Despite a number of different causes (viral infections, stroke, neoplastic disorders, genetic mutations, trauma, and epigenetics [chemicals effecting genes—see Chapter 3, page 62]), neuronal damage is most frequently associated with chronic activation of an innate immune response in the CNS.

It has become well established that the immune system is inextricably involved in shaping the brain during development as well as mediating damage during aging. Intense research is being conducted on these neuroimmune interactions during development and disease (immunosenescence). A better understanding of this bidirectional neuroimmune crosstalk (discussed further on page 82) will be key to manipulating these responses and developing effective immunotherapies to reduce the impact of neurodegenerative diseases. Some of these diseases

include Alzheimer's, Parkinson's diseases, amyotrophic lateral sclerosis (ALS), Huntington's disease, spinocerebellar ataxia, brain trauma, epilepsy, multiple sclerosis, and senile dementia [15].

6. Clinical diagnosis and treatment of chronic inflammation

6.1. Diagnostic strategies

As opposed to acute inflammation, chronic inflammation can be difficult to identify, especially in situations where no precipitating cause (acute inflammation, antigenic or otherwise) exists. Given the all-inclusive nature of chronic inflammation as an immunologic disease, its diagnosis can be organ-specific or disseminated among multiple body systems (see Fig. 4.2). The diagnostic evaluation includes a thorough history, physical examination, laboratory testing, and imaging based on suspected organ-system involvement(s). In all the cases, signs and symptoms can vary widely.

Nonspecific symptoms associated with chronic inflammation include

- Body pain, arthralgia, myalgia;
- Chronic fatigue and insomnia;
- Depression, anxiety and mood disorders;
- Gastrointestinal complications like constipation, diarrhea, and acid reflux;
- Weight gain or weight loss;
- Frequent infections;
- Fatigue;
- Fever;
- Mouth sores;
- Rashes;
- Abdominal pain;
- Chest pain.

Generally speaking, patients with chronic diseases can be somewhat de facto assumed to have some degree of chronic inflammation [16]. The Center for Disease Control (CDC) defines chronic diseases as “conditions that last one year or more and require ongoing medical attention or limit activities of daily living or both.” [16] Chronic diseases such as heart disease, cancer, and diabetes also are the leading causes of death and disability in the United States and are the leading drivers of the nation's $3.5 trillion in annual healthcare costs [17]. No surprise when considering the prevalence of chronic diseases. Six in 10 adults in the US. have a chronic disease. Four in 10 have two or more (comorbidities). While there are significant numbers of disease states that can be classified as chronic, Table 4.4 lists the 10 most common chronic conditions ranked by death rate [18] (this 2019 table does not consider COVID-19 which became the

third leading cause of U.S. death in 2020). Such prioritized lists vary based on demographic factors (i.e., age, gender, race, geographic location, and socioeconomics). Notwithstanding such demographic considerations, as mentioned previously (and pretty frequently by now), "… chronic inflammatory disease is the progenitor or originating cause of *all* the major chronic disease categories."

Not included in Table 4.4 of chronic diseases is obesity (BMI $>25 mg/kg^2$). When given the CDC's BMI definition of chronic disease and current epidemiological data on obesity (prevalence, 40.0% among young adults aged 20–39 years, 44.8% among middle-aged adults aged 40–59 years, and 42.8% among adults aged 60 and older) as well as an increase of 11.9% from 1999 to 2018 [19], obesity must be considered a chronic disease, perhaps the leading chronic disease. Unfortunately, this major disease risk factor (obesity) associated with chronic inflammation significantly increases the morbidity and mortality of chronic diseases and now, particularly with Covid-19 [20] (more discussion on this in Chapter 7). The prevalence of comorbidities with obesity reach levels as high as 52.3% with common conditions such as hypertension and diabetes and a corresponding increase in the mortality rates [21].

Table 4.4

1. Heart disease (death rate 23.0%);
2. Cancer (death rate 21.3%);
3. Unintentional injury (death rate 6%);
4. Respiratory diseases including asthma and COPD (death rate 5.7%);
5. Stroke and cerebrovascular disease (death rate of 5.2%);
6. Alzheimer's disease (death rate of 4.3%);
7. Type 2 diabetes (death rate 3%);
8. Influenza and pneumonia (death rate 2%);
9. Kidney disease (death rate 1.8%);
10. Chronic liver disease and cirrhosis (death rate 1.8%)

Ten Most Common Chronic Conditions (ranked by death rate).

Source: National Vital Statistics Reports. June 24, 2019. 68(6).

Unfortunately, there are no absolute, specific laboratory tests to assess patients for chronic inflammation. In fact, such tests are generally undertaken when the inflammation occurs in association with another medical condition (comorbidity). Some of these laboratory tests include serum protein electrophoresis, C-reactive protein, erythrocyte sedimentation rate, and human leukocytic antigen assessment.

6.2. Treatment (immunotherapies)

Chronic inflammation and autoimmune diseases often require treatment directed at the specific tissue(s) and organ system(s) being adversely affected or, in the case of diffuse disease, treated in a broader, more systemic approach. Some of the organ/tissue-specific treatments and procedures are delivered as targeted strategies directed to the effected organs (e.g., antithyroid medications for Grave's disease) or tissues (e.g., topical corticosteroids for psoriasis). In the case of diffuse multiorgan conditions like cancers, type-1 diabetes, and many of the autoimmune diseases, more generalized treatments are classified as immunosuppressive and immunomodulating (suppressing or stimulating) therapies, referred to as "nonspecific therapies." These therapies include types of drugs that are used to suppress dysregulation of the immune system in chronic inflammation, auto-antigenicity in autoimmune diseases, or to boost the immune system response in cancers and antitumor therapies. Immunization and vaccine approaches can also be considered immunotherapies for infectious and autoimmune diseases [22].

Recent research (2021) [23] has identified a large family of cell surface proteins (G-protein-coupled receptors or GPCRs) which are key molecules within the complement system of the immune system (see Chapter 1, page 18). These GPCR molecules have the potential to combat inflammation by binding with β-arrestin 1 and 2 (Barr), a family of multifunctional intracellular proteins. By designing ligands (molecules that binds to another molecule—more on ligands in Chapter 6 on cancer), preferential coupling can be induced between GPCR and a "decoy receptor" (DR6) to produce robust Barr protein recruitment leading to biased signaling ("biased agonism"). This process is a novel and effective immunologic method to treat chronic inflammation.

But, notwithstanding the different uses of immunotherapies and even immune-related cellular and genetic procedures (stem cells transplantation, CRISPR, CAR-T to be discussed in Chapters 5–7), they all represent "a distinction without a difference." That is to say, all the diagnostic entities being addressed (inflammation, autoantigenicity, autoimmunity, cancers, and tumors) have as their pathogenic basis, chronic inflammation. Thus, we can say that, notwithstanding the distinct clinical diagnosis, ultimately we are effectively treating chronic inflammation.

So broadly speaking, the treatments for chronic inflammation (*aka* autoimmune diseases) would include the following:

- Nonspecific therapies;
- The biologics;
- Corticosteroids and NSAIDs;
- DMARDs;
- Checkpoint inhibitors;
- Monoclonal antibodies;
- Immunogenetics and immunogenomics;

- ○ CAR-T
- ○ CRISPR-Cas9
- ○ CRISPR-Cas13
- ○ mRNA therapy
- ○ Transplant therapy

• Regenerative medicine (stem cell transplantation)

To keep this rather broad subject of treatment of chronic inflammation organized (I hope), I would like to postpone a full discussion of all the immunotherapies and related drugs and procedures to Chapter 5 on autoimmune diseases. I think by now you can appreciate the relative indistinguishable nature of chronic inflammation and autoimmune disease. So, keeping the discussion of the similar treatments for both might fit best in Chapter 5's comprehensive discussion (next up) on autoimmune diseases. I hope you will feel the same as you read Chapter 5.

7. Neural downregulation of the immune system and chronic inflammation

As we have described throughout Section 1, “removal of the cause” is the most effective means of modulating, suppressing and reversing inflammation. We also described four specific mechanisms that produce positive effects in adaptive immunity (Chapter 2, page 26), one of which was “downregulation” through neuroendocrine and neurogenic pathways. As you will see going forward in Section 2, sometimes “removal of the cause” is not a feasible therapeutic strategy by virtue of the pathophysiologic nature of chronic inflammation and no less, the prevalent etiology of autoimmune-related chronic inflammation being “self” (and thus, not removeable). Nonetheless, the body is constantly striving to maintain or reestablish homeostasis and so too is the case with chronic inflammation. In such cases, the neurological system becomes the main player in a highly complex (you didn't expect anything less now, did you?) set of molecular and chemical actions and reactions to downregulate (reduce or suppress a response to a stimulus) the immune system.

Starting with the release of immune mediators and cytokines resulting from innate immune responses (e.g., signals 1 and 2) triggered by neuronal stimuli, this humoral/cellular and neural complex amplifies local responses into inflammation (you might review Figs. 1.4 through 2.1). These systemic neuroendocrine and bidirectional neural responses result, in most cases, in a resolution of the immune process (i.e., acute inflammation) and restoration of the normal homeostatic state. The brain has immune microglia, macrophages, and dendritic cells that can produce cytokines and prostaglandins in response to inflammatory stimuli that can stimulate neural and nonneural brain cell receptors [24]. The sympathetic nervous system amplifies immune cell activity and makes bidirectional systemic immune responses possible, while the parasympathetic nervous

system (PNS) and the hypothalamic–pituitary–adrenal (HPA) axis generally inhibit chronic inflammation. However, cortisol, a glucocorticoid, is the end product of the HPA axis and stimulates the hypothalamus to release adrenocorticotropic hormone (ACTH) from the anterior pituitary. ACTH stimulates the adrenal cortex to also produce cortisol. Negative feedback on glucocorticoid receptors in the hippocampus can cause cortisol to stop the further release of CRH and ACTH and various others that can modulate the HPA-axis and nuclear factor-kappa B (NF-κB) which increases proinflammatory mediators [25]. In a well-regulated system, immune cells express glucocorticoid receptors allowing cortisol to inhibit immune cell activation and proinflammatory cytokine release [26]. (I hope you were able to follow the infamous bouncing ball on that sequence.)

It has been known for decades that dysregulation of the HPA-axis is associated with depression. Major depressive disorder and depressive symptoms are associated with chronic inflammation [27]. Uncontrolled or dysregulated immune cells, due to prolonged and exaggerated stress activation may be a factor of greater NF-κB (Nuclear Factor κB,a protein transcription factor) activity due to reduced cortisol sensitivity. Cytokines influence the production and metabolism of neurotransmitters such as serotonin and dopamine which play critical roles in mood. These effects can be mitigated with antidepressant serotonin inhibitors combined with nonsteroidal antiinflammatories [28].

Sympathetic innervation links the brain directly to the adrenal medulla and the “fight-or-flight” phenomenon (increases heart rate, blood pressure, and breathing rate and diverts blood from nonessential organs to the major muscle groups and the brain). Upon sympathetic activation, the adrenal medulla releases catecholamines, epinephrine, and norepinephrine which can lead to immune dysregulation through proinflammatory cytokine production and enhance systemic inflammation. The vagus nerve of the PNS has afferent and efferent nerve fibers for bidirectional communication between the brain and periphery through release of acetylcholine. The acetylcholine molecules can then bind to the α7 nicotinic acetylcholinergic receptor (nAChR) on an immune cell's surface and inhibit inflammatory expression, resulting in decreased cytokine production and antiinflammatory effects [29].

The neural response to inflammation is usually rapid and can have an amplifying or dampening effect on the inflammatory process. But overall, these neural response patterns aim to maintain normal physiological homeostasis in response to immune system stimulation and the restoration of normal tissue function. (Remember in Chapter 1 when I mentioned that neurologists and brain surgeons could argue equal complexity with immunologists? This last section kind of makes that case.)

8. Brief research summaries on chronic

inflammation

(Reference citations for each research study presented below can be found in the corresponding footnote. Also, a listing of available scientific reference sources and databases used by the author are included in the book's Acknowledgments.)

1. Postulating a “universal” disease theory, namely, identifying chronic inflammation at the magnitude of being the basis of *all* disease, as I have in this chapter, can easily be misinterpreted as an overzealous statement of the breadth and depth of chronic inflammation. To address such reasonable doubt, let's use immunoinformatics to defend the thesis by quoting a few perspectives on chronic inflammation from among thousands of authoritative journal articles over the past few years:

    - Chronic inflammatory diseases are the most significant cause of death in the world [30].
    - Schofield A. Inflammation: The Root of All Disease. Vitalfit Collective. January 10, 2019.
    - “… inflammatory processes are involved in not just a few select diseases, but a wide variety of mental and physical health problems that dominate present-day morbidity and mortality worldwide” [31].

    - “Indeed, chronic inflammatory diseases are the most significant cause of death in the world today, with more than 50% of all deaths being attributable to inflammation-related diseases” [32].
    - “Today, chronic inflammatory diseases are at the top of the list of death causes.” Medical Press. January 29, 2020.
    - World Health Organization (WHO) ranks chronic diseases as the greatest threat to human health [4].
    - “… excessive inflammation is a common thread in all forms of disease development and progression” [33].

Thus, per our stated paradox, immunology (specifically, chronic inflammation) can be “our worst enemy.” Sadly, COVID-19 is a painful example of this incongruity (see Chapter 7).

2. You'll notice in Table 4.4 that cancer is one of the leading chronic diseases (#2) associated with chronic inflammation. Of course, it is well established that the fundamental cause of cancer relates to genetic mutation(s) as will be discussed in Chapters 5 and 6, but chronic inflammation is its resultant tissue and organ pathology. Thus, we will be addressing therapeutic

technologies that are being used in chronic inflammation (and autoimmune diseases) extensively and in cancer treatment as well. In fact, because of its high degree of incidence and prevalence, all immunotherapeutic agents (i.e., the biologics and nonspecific agents) presented in this Chapter's discussion as well as the immunogenetic and genomic therapies (to be addressed in Chapter 5) are all being applied to cancer at the clinical and research levels [34].

3. One interesting immunotherapeutic approach named the "idiotype network theory (INT)" is receiving considerable attention in recent years. It pertains to the reference made back in Chapter 2 (page 26) about "… the very complex system of idiotype antigen-specific B cells," also referred to as the "idiotype network theory (INT)." It is being studied extensively as a potential cancer immunization therapy. We'll revisit it once more in the Chapter 6 section on cancer research [35].
4. Antitumor necrosis factor (anti-TNF) drugs are an important second-line treatment for rheumatoid arthritis after methotrexate. However, patient heterogeneity hinders identification of predictive biomarkers and accurate modeling of anti-TNF drug responses. A study was conducted to investigate the usefulness of machine learning to assist in developing predictive models for treatment response. Using data on patient demographics, baseline disease assessment, treatment, and single-nucleotide polymorphism array from the "Dialogue on Reverse Engineering Assessment and Methods (DREAM): Rheumatoid Arthritis Responder Challenge," a Gaussian process regression model was developed to predict changes in the Disease Activity Score in 28 joints for patients and to classify them into either the responder or the nonresponder group. The method predicted changes and correctly classified responses from 78% of patients. Gaussian process regression effectively remapped the feature space and identified subpopulations that do not respond well to anti-TNF treatments. This was the best-performing model in the DREAM Challenge [36].
5. Using common noninvasive techniques for body composition assessment methods (computed tomography [CT], magnetic resonance imaging [MRI]) images extracted by these methods can be processed with artificial intelligence and radiomic analysis. The idea is to search for features that may be extracted from medical images (CT and MRI), and that may turn out to be good predictors of metabolic disorder and chronic diseases like obesity and cancer. This could lead to patient-specific treatments and management of several diseases linked with excessive body fat [37].

Chapter highlights (key points and paradoxical-related information)

1. Inflammation progresses from acute to chronic when the acute form is prolonged due to incorrect or misdiagnosis; congenital or acquired mutations; chronic exposure to certain environmental factors; accumulating inflammatory byproducts; disruption to homeostasis; autoantigenic factor; or “rogue B cells" and epitope spreading.
2. Chronic inflammation is driven by hypersensitivity or Type I to IV “over-reactions” initiated during innate immunity and advanced through proinflammatory mediators in the inflammatory cascade.
3. Histopathology and pathophysiology of chronic inflammation differ from acute inflammation through increased WBC cellular activity (particularly neutrophils), giant cells, granulomas, fibroblasts, fibrinization, caseation, necrosis, and tissue (and proteomic, DNA) destruction, especially in blood vessel walls (perivasulitis).
4. The pharmacodynamics of the inflammatory cascade advance through proinflammatory cytokines, chemotactic factors, enzymes, hormones, proteoglycans and reactive molecules (ELAMs) controlled by complex neurogenic and non-neurogenic mechanisms.
5. A multitude of paradoxical therapeutic variables producing proactive and inhibitory effects (e.g., TNF’s inflammatory effects while still protecting its beneficial anti-infection and anti-cancer properties) require orchestration of numerous biologics to maximize inflammatory inhibition (immunosuppression) while stimulating (immunomodulating) selective beneficial cytokine, chemokine, enzymatic and cellular immunologic components.
6. The vast array of diseases in diffuse systemic and organ specific categories as well as all chronic diseases are forms of chronic inflammation (diseases ending in “…itis”).
7. The etiologies associated with chronic inflammation, specifically disruption to homeostasis; autoantigenic factor; and “rogue B cells" and epitope spreading, make it synonymous with autoimmune disease. In effect, autoimmune diseases can be considered varying forms of chronic inflammation (more in Chapter 5).
8. Because of its diffuse pathogenic effects, particularly its effects on the all-inclusive systemic vascular system, chronic inflammatory disease is considered (by this author) to be the progenitor or originating cause of *all* the major human disease categories. How about “*pathomelitis*” as a better descriptive label for it?

9. Immunotherapies (immunosuppressive and immunomodulating therapies) are "non-specific therapies" referred to as "biologics" (intrinsic bodily agents) that include types of drugs like DMARDs, biologics, monoclonal antibodies, checkpoint inhibitors, etc. used to suppress dysregulation of the immune system by modulating the immune response in chronic inflammation including cancers and anti-tumor therapies.
10. Genetic procedures (stem cells transplantation, CRISPR, CAR-T, all discussed in Chapters 5, 6 and 7) are all considered immunotherapies as well as immunization and vaccine approaches for infectious and autoimmune diseases (all in essence, forms of chronic inflammation)

References

1. Bennett J.M, Reeves G, Billman G.E, et al. Inflammation-Nature's way to efficiently respond to all types of challenges: implications for understanding and managing "the epidemic" of chronic diseases. *Front Med* . 2018;5:316.
2. Cimons M. *Chronic inflammation is long lasting, insidious, dangerous. And you may not even know you have it* . Washington Post Health; 2020.
3. Serhan C.N, Ward P.A, Gilroy D.W. Fundamentals of inflammation. *Yale J Biol Med* . 2011;84(1):64–65.
4. Han S. *World Health Organization (WHO) ranks chronic diseases as the greatest threat to human health* . HealthLine; July 27, 2018.
5. *Proinflammatory cytokine list* . Sino Biological; 2020.
6. Pahwa R, Goyal A, Bansal P, et al. *Chronic Inflammation* . StatPearls; 2020 [Internet].
7. Furman D, Campisi J, Verdin E, et al. Chronic inflammation in the etiology of disease across the life span. *Nat Med* . December 25, 2019(12):1822–1832.
8. Baudouin C, Kolko M, Melik-Parsadaniantz S, et al. Inflammation in Glaucoma: from the back to the front of the eye, and beyond. *Prog Retin Eye Res* . July 2021;83:100916.
9. Heart Disease and Stroke Statistics. Update: a report from the American Heart Association. *Circulation* . January 31, 2019;139:e56–e528. .
10. Ridker P.M, Rane M. Interleukin-6 signaling and anti-interleukin-6 therapeutics in cardiovascular disease. *Circ Res* . May 17, 2021;128(No. 11).
11. Luigi M, Biasucci L.M, Pedicino D, Liuzzo G. Promises and challenges of targeting inflammation to treat cardiovascular

disease: the post-CANTOS era. *Eur Heart J* . 2020;41:2164–2167.
12. Goldberg E.L, Dixit V.D. Drivers of age-related inflammation and strategies for healthspan extension. *Immunol Rev* . 2015;265:63–74. doi: 10.1111/imr.12295.
13. Woods J.A, Wilund K.R, Martin S.A, Kistler B.M. Exercise, inflammation and aging. *Aging Dis* . 2012;3:130–140.
14. Limanaqi F, Biagioni F, Gaglione A, et al. A sentinel in the crosstalk between the nervous and immune system: the (Immuno)-Proteasome. *Front Immunol* . March 29, 2019;10:628.
15. Shouman K, Benarroch E.E. Peripheral neuroimmune interactions: selected review and some clinical implications. *Clin Auton Res* . August 31, 2021:477–489.
16. About Chronic Diseases, . *National Center for Chronic Disease Prevention and Health Promotion* . CDC; October 23, 2019:16.
17. GBD 2017 Causes of Death Collaborators, . Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study. *Lancet* . 2018;392:1736–1788.
18. Heron M. Division of vital Statistics. Deaths: leading causes for 2017. *Natl Vital Stat Rep* . June 24, 2019;68(6).
19. CDC. *Adult obesity facts. Division of Nutrition, physical activity, and obesity* . National Center for Chronic Disease Prevention and Health Promotion; June 29, 2020.
20. Pennington Biomedical Research Center, . *Why is obesity so common in COVID-19 patients?* Medical Press; July 24, 2020.
21. Nguyen N.T, Magno C.P, Lane K.T, et al. Association of hypertension, diabetes, dyslipidemia, and metabolic syndrome with obesity: findings from the National Health and Nutrition Examination Survey, 1999 to 2004. *J Am Coll Surg* . 2008;207(6):928–934.
22. Mandal A. *Autoimmune disease development of therapies* . News Medical Life Science; May 29, 2019.
23. Pandey S, Kumari P, Baidya M, et al. *Intrinsic bias at non-canonical, β-arrestin-coupled seven transmembrane receptors* . Molecular Cell; September 27, 2021 (in press).
24. Wrona D. Neural-immune interactions: an integrative view of the bidirectional relationship between the brain and immune systems. *J Neuroimmunol* . 2006;172:38–58. doi: 10.1016/j.jneuroim.2005.10.017.
25. Barnes P.J, Karin M. Nuclear factor-kappaB: a pivotal transcription factor in chronic inflammatory diseases. *N Eng J*

Med . 1997;336:1066–1071.
26. Sapolsky R, Krey L, McEwen B. Glucocorticoid-sensitive hippocampal neurons are involved in terminating the adrenocortical stress response. *Proc Natl Acad Sci USA* . 1984;81:6174. doi: 10.1073/pnas.81.19.6174.
27. Bremmer M.A, Beekman A.T, Deeg D.J, et al. Inflammatory markers in late-life depression: results from a population-based study. *J Affect Disord* . 2008;106:249–255. doi: 10.1016/j.jad.
28. Raison C.L, Miller A.H. Is Depression an inflammatory disorder? *Curr Psychiatry Rep* . 2011;13:467–475.
29. Tracey K.J. Physiology and immunology of the cholinergic anti-inflammatory pathway. *J Clin Invest* . 2007;117:289–296. doi: 10.1172/JCI30555.
30. Pahwa R, Jialal I. *Chronic inflammation* . StatPearls; 2019.
31. *National Center for Biotechnology Information* . U.S. National Library of Medicine; December 25, 2019. .
32. *Washington Post health* . January 2020.
33. Han S. *World Health Organization (WHO) ranks chronic diseases as the greatest threat to human health* . Bennett: HealthLine; July 27, 2018:1.
34. Kumar A, Swain C.A, Shevde L.A. Informing the new developments and future of cancer immunotherapy. *Cancer Metastasis Rev* . 2021;40:549–562.
35. Kohler H, Pashov A, Kieber-Emmons T. The promise of anti-Idiotype revisited. *Front Immunol* . March 26, 2019;10:808.
36. Lee A.Y, Ewing A.D, Ellrott K, et al. Combining accurate tumor genome simulation with crowdsourcing to benchmark somatic structural variant detection. *Genome Biol* . 2018;19:188.
37. Attanasio S, Forte S.M, Restante G, et al. Artificial intelligence, radiomics and other horizons in body composition assessment. *Quant Imaging Med Surg* . March 10, 2020;10(8):1650–1660.

5: Autoimmune disease

when *self* becomes the villain

Abstract

As more is learned about the human immune system and its benefits and liabilities to health and well-being, definitive identification of a malevolent portion of the system known as autoimmunity results in a wide-ranging category called autoimmune disease (“our worst enemy”). These conditions present with the characteristic signs of chronic inflammation and follow a chronic, unremitting course. Most are still a mystery and occur (greater in women by 2 to 1) when, for an array of currently unknown reason(s), the system doesn't seem to distinguish self from nonself (“the paradox of the immune system”). Elusive “autoantigen” (autoantigenicity) theories abound including a prolonged inflammatory process, a patient's genome, environmental stimulants, accumulation of proinflammatory cytokines, X chromosome factors, “rogue B cells” epitope spreading, and even the microbiome. Classifications range from specific tissue or organ system involvement to indiscriminate, diffuse, multisystem afflictions. The use of immunopharmacologic therapies (biologics, cytokines, monoclonal antibodies, checkpoint inhibitors), gene editing (CRISPR-Cas9), gene replacement (CAR-T), stem cell transplantation (regenerative medicine), and transplant therapies is described and discussed.

Keywords

Autoantigen; Autoimmunity; Biologics; Checkpoint inhibitors; Cytokine; Epitope spreading; Genome; Immunotherapy; Microbiome; Monoclonal antibodies; Rogue B cells

> *She walked with the universe on her shoulders and made it look like a pair of wings.*
>
> *Ariana Dancu*

1. Introduction

Now we begin to add more drama to “the paradox of the immune system.”

Antigens, by definition, are “foreign.” But as we learn more about the

immune system, it has become apparent that “foreign” may not be entirely synonymous with “nonself.” When, for some unknown reason, the body incorrectly identifies itself (i.e., self) as foreign (i.e., nonself), effectively, the body becomes an “antigen” and generates a process referred to as “autoantigenicity.” This process initiates an adaptive immune response directed at … *you got it*—itself. Stated another way, the immune system has the potential to produce an “autoimmune response.”

2. Female predilection for autoimmune disease

Autoimmune disease develops after immune dysregulation in both the innate and adaptive immune systems. This category of immune diseases occurs in females at a rate of two to one over males (6.4% of women vs. 2.7% of men) [1]. In fact, it is estimated that 78% of people affected with autoimmune diseases are women [2]. There are an abundance of theories as to why there is such a strong female predilection to autoimmune diseases. Some are based on speculation, but most on evidence-based science [3]. A listing (and labeling) of some of those possible causes include:

- Male testosterone protection (speculation);
- Pregnancy factors (evidence-based science);
- Gene expression (evidence-based science);

- Embryologically, women confer first immunity to their babies suggesting a stronger immune system than the father (evidence-based science);
- “Pregnancy brain” (I mentioned this back in Chapter 1, page 5) where fetal cells from the embryo transfer to the mother during pregnancy and remain in her brain for life producing a “potential” autoantigenic effect (evidence-based science and speculation);
- Women, as traditional caregivers, suggest a kind of phylogeny (evolutionary development of women seems to produce more absolute lifelong antibody levels than men) thus producing a stronger immune system but increased risk for innate immune dysregulation (speculation);
- Females tend to have more body fat than males, thus more immune cells (evidence-based science);
- Women live longer, thus producing more antibodies that contribute to the longer life, but also create a greater potential risk for dysregulation and abnormal homeostasis (speculation);
- The “hygiene hypothesis” (see page 60) which compromises the microbiome and increases the risk of autoimmune disease (greater in females due to sexual dimorphism) (evidence-based

and speculation);
- Probably more theories abound, including any you might think of and certainly, the topics of discussion presented in the balance of this chapter.

2.1. XCI (lyonization)

Perhaps the most credible and validated, science-based theory regarding female bias in autoimmune diseases lies in the immunogenomic science we have introduced in Chapters 1 (page 5) and 3 (page 58), that is the X chromosome inactivation (XCI) or "lyonization" and its intimate relationship with microRNA. From this validated hypothesis, a number of explanations for female predilection for autoimmune diseases have evolved. One such explanation suggests that about 15% of genes escape the XCI process (called "escapees"), including among them CD40L, CD99, LAMP-2, IRAK-1, TLR7, USP27X, DDX3X, CXORF21, and XIAP (some of the ones I asked you to remember from Chapter 1—yeah, right!), all of which recent research has confirmed as primary attributions to the female bias of autoimmune diseases, especially SLE [4]. These escapees also play a significant role in oncogenesis (cancer production) and will be further discussed in Chapter 6, page 158.

It is well understood that sex hormones are an enormous factor in the regulation and dysregulation of immunity. Predominant influences of female estrogen and progesterone both increase and decrease proinflammatory mediators and are believed to be responsible for autoantibody development, autoimmune stimulation, and corresponding autoimmune diseases [5]. More so, perhaps, estrogens regulate microRNAs (miRNA), the noncoding RNA gene abundant on the female X chromosome and essential in gene expression (as mentioned in Chapter 3). This relationship of the X chromosome, in combination with XCI and XCI "escape," provides the basis of "protection" (vs. risk) for females against certain cancers and an increased risk for males (yet another immune paradox) [6]. This paradox of the complex XCI immune phenomenon will be revisited once more in Chapter 6. But after all is said and done regarding definitive causes of autoimmune diseases (and cancers), understanding their etiologies remain relatively nascent and will require an enormous amount of continuing research.

3. Theories on the pathogenesis of autoimmune diseases [7]

There are several theories as to the cause(s) of the idiosyncratic autoimmune responses that we will examine. But whatever the cause(s), the response has created an entirely separate disease category referred to as "autoimmune disease." Table 5.1 reveals an impressive (and ominous) list of some (28 from about 80 plus) prevalent autoimmune diseases. As mentioned previously in Chapter 3 and just above, despite the fact that the

etiology of this disease category remains unknown or at least open to multiple hypotheses, its pathogenesis (development) and thus, its therapeutic strategies are similar to those of chronic inflammation in that chronic inflammation is the immunological basis and process responsible for autoimmune diseases. Thus, rather than repeating extended descriptions of the pathogenesis and immunotherapies of chronic inflammation presented in Chapter 4, I will be referring (numerous times) throughout this Chapter back to Chapter 4, Chronic inflammation: The "ultimate enemy."

The cause(s) of autoimmune diseases remain unknown, but research has strongly suggested a pathogenesis ("natural history") of the disease progressing over time and insidiously producing its damage. The path of the disease includes five possible (probable?) causes (Table 5.2) which I'm sure you will recall their similarities from our Chapter 4 discussion (and Table 4.1, page 73) regarding the etiologies of chronic inflammation. As discussed in Chapter 4, the etiologies of autoimmune diseases and those of chronic inflammation are virtually identical, thus making the two entities synonymous, one with a clinical label (autoimmune disease) and one as a pathological classification (chronic inflammation). Now, let's examine both of them a little more closely as to their suppositions and their factual basis.

Table 5.1

- **Alopecia areata**
- **Ankylosing spondylitis**
- **Antibody syndrome**
- **Antiphospholipid**
- **Autoimmune hepatitis**
- **Bullous diseases**
- **Celiac disease**
- **Cicatricial pemphigoid**
- **Dermatomyositis**
- **Giant cell arteritis**
- **Goodpasture's disease**
- **Graves disease**
- **Guillain-Barre syndrome**
- **Hashimoto's disease**
- **Idiopathic thrombocytopenic purpura**
- **Inflammatory bowel disease**
- **Juvenile arthritis**
- **Lupus erythematosus (SLE)**
- **Mixed connective tissue disease**
- **Multiple sclerosis**
- **Myasthenia gravis**
- **Pemphigus vulgaris**
- **Polymyalgia rheumatica**
- **Polymyositis**
- **Primary biliary cirrhosis**
- **Psoriasis**
- **Rheumatoid arthritis**
- **Scleroderma**
- **Sjogren's syndrome**
- **Takayasu's arteritis**
- **Temporal arteritis with polyangiitis**
- **Uveitis**
- **Vitiligo**
- **Wegener's granulomatosis**

Listing of prevalent autoimmune diseases.

Source: Foundations of AI in Healthcare and Bioscience; Catania; Academy Press. November 2020.

Table 5.2

1. A prolonged inflammatory process from failure to eliminate an antigen;
2. Patient's genome;
3. Environmental factors;
4. Increasing release and accumulation of proinflammatory cytokines;
5. Abnormal immune response to self through “rogue B cells” and epitope spreading

Theories on etiologies and pathogenesis of autoimmune disease.

Source: Foundations of AI in Healthcare and Bioscience; Catania; Academy Press. November 2020.

3.1. A prolonged inflammatory process from failure to eliminate an antigen

If everything in this world that is not “self” is antigenic to self, based on the discussion in Chapter 2, it would seem both logical and mathematical that the overwhelming percentage of antigenic attacks on self are controlled by our innate (natural) immunity (remember, our “friend?”). Occasionally, however, antigens are not removed in a timely fashion or continually reoccur through reexposure, an example of which would be a persistent allergen (seasonal or otherwise). Inability to remove an antigen will continually stimulate the innate immune system with resultant accumulating cellular, humoral, molecular byproducts that begin to trigger the adaptive immune response. Notwithstanding a powerful and inclusive innate defense system, pathogenic antigens can breach this immune barrier and result in the adaptive immune response (discussion from Chapter 2). Some of those pathogens prove to be virulent enough to resist or even overcome the body's adaptive response. In such cases, the immune system continues to “fight the fight,” the results of which produces prolonged chronic inflammation (discussion from Chapter 4) and the clinical sequalae of that prolonged process resulting in clinical damage to tissue(s) and organ(s) systems (as found in autoimmune disease).

Here's an ideal place to revisit the concept of “stress antigens” that we mentioned a number of times in previous chapters. A nonsubstance entity like mental, emotional, physiological, or physical (injury) stress can disrupt the normal homeostasis (maintenance of a stable balance) of the immune system, and thus, is interpreted as “nonself” (admittedly, non-substance) [8], “foreign” or technically, an antigen. Now with that in mind, think back to “ulceration” in the acute inflammatory cascade from Chapter 2, page 31. Remember how an acute inflammatory reaction (from a demonstrable antigen) without proper care can lead to the destruction and loss of healthy tissue, eventual scarring, functional loss (“functio laesa”), and even DNA disruption? When we extended that dysregulated process to chronic inflammation (Chapter 4, page 88), we added caseation

(cheesy textured tissue), necrosis (dying tissue) and apoptosis (programmed cell death) disruption, and an accumulation of toxic byproducts.

All of these inflammatory (acute and chronic) disturbances in the immune system cause a dysregulation in homeostasis “or stress” on the system. This physiological stress can be considered an autoantigen that began with an antigenic reaction and eventually generated a cycle of autoantigenicity (from homeostatic imbalance inciting neurogenic and neuroendocrine reactions) collectively referred to as a “clinical autoimmune cycle” (Fig. 5.1—diagram #8: yet another addition to our growing immune system flow diagram—and we're not done yet).

3.2. Patient's genome

Abnormalities (inherent or mutational) in the patient's genome can make it susceptible to dysregulation. People's genes are what “predispose” or provide them with a genetic susceptibility to dysregulate the immune system. This in turn yields chronic inflammation and, in effect, creates the pathologic damage to cells, tissues, and organ systems synonymous with autoimmune diseases. Almost every aspect of the immune system contributes to the pathogenesis of autoimmunity. Complicated interactions between genetic variants, epigenetics (nonaltered DNA modifications of phenotype gene expression) and environmental factors produce a multitude of pathways that lead to autoimmune diseases [9]. (More discussion on genetics, the genome, and autoimmunity below.)

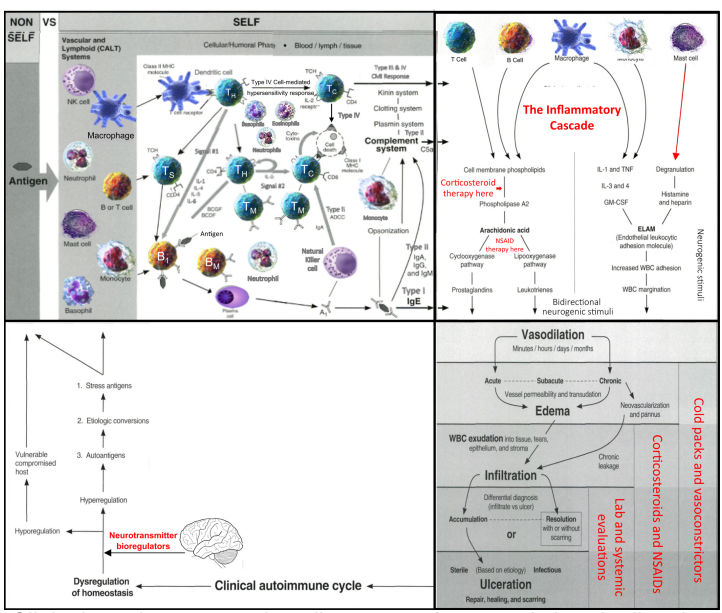


Figure 5.1 Clinical autoimmune cycle—diagram #8.Acute and chronic disturbances in the

immune system secondary to the inflammatory cascade cause a dysregulation in homeostasis leading to an autoantigenic (created by “self”) stimulus producing a clinical autoimmune cycle (note this cycle is an addition to the growing immune system flow diagram starting with the APC diagram back in Chapter 1, Fig. 1.3). Source: Louis J Catania © 2022.

3.3. Environmental factors

Endogenous (internal) autoantigens include such things as metabolic and immune byproducts, “rogue B cells” and epitope spreading (discussed below), stress, genetic mutations, etc. However, most antigens we encounter are external, “nonself” substances that the body may interpret as toxic. Pollution, allergens, pathogens, mechanical or physical injury or irritation, smoking, chemicals, insect bites, stings, etc. all can be considered environmental factors or antigenic toxins as discussed in Chapters 1 and 2. In combination with the inherited alleles that an individual possesses for a specific gene (the genotype), a given environmental factor can produce a “phenotype trigger” to produce the clinical manifestations of autoimmune disease.

Consider the person who has smoked all their life without ever experiencing the classic, associated diseases (respiratory, cardiovascular, carcinogenic). One (like an aging, inveterate smoker) would use this as an argument that smoking is not a risk factor. On the contrary, that individual “rolled the dice” (unknowingly) on not having the specific gene(s) and alleles to induce a smoke-related disorder, and he/she won. But epidemiologic studies have unequivocally concluded that there is a greater risk of having one or more “phenotype triggers” for smoking induced disorders than not. Of course, this applies to all environmental factors as well.

But the free-will choices we make regarding what we will or will not expose ourselves to (i.e., risks) range from people's common sense (or lack thereof) to practicing good personal and public health measures (e.g., smoking, or of late, wearing a mask, and a vaccination during an infectious pandemic). Indeed, the environmental factors we choose differ considerably from the ones our genes choose for us (from allergies to infections to cancers). Heredity patterns and DNA testing (karyotypes) tell us a great deal about these environmental risks, some obvious, and some buried in our genome. (Maybe generalized DNA screening as a preventive health measure, or at very least a diagnostic tool, might be worthwhile? I believe it is and I hope we will see it as routine in the future. But again, its ethical implementation will be a “buyer beware” situation, if not tightly regulated.)

3.4. Increasing release and accumulation of proinflammatory cytokines

As the immune system fights off foreign antigens, it is continually

releasing inflammatory proteins called “proinflammatory mediators.” If the pathological antigen is not successfully eliminated in a timely fashion, these proinflammatory mediators accumulate in the tissue and, by virtue of their abnormally large detritus, they are interpreted by neurogenic pathways (see page 87) and by the adaptive immune system as antigenic (foreign). This perpetuates an autoimmune response. As described previously, this phenomenon of an accumulation of inflammatory cytokines was highlighted in Chapter 2 (page 31) in the discussion of acute inflammation and “dysregulation” of the immune system. In that instance we talked about heat generation by pyrogenic mediators (particularly interleukin that produces a “leukocytic pyrogen” as a byproduct) resulting in “calor” and fever (increased body and tissue temperature) as a classic inflammatory feature. The overabundance of these pyrogenic mediators create overly aggressive immunogenic signals that produce an “attack” on the body (another paradox) rather than beneficial, communicating signals of the inflammatory process [10]. This could generate an antigenic response, or more appropriately termed an “autoantigenic, autoimmune response,” yet another source of a “clinical autoimmune cycle” as described above and in Fig. 5.1.

3.5. Abnormal immune response to “self” through “rogue B cells” [11] and epitope spreading [12]

Autoimmune disease can simply be stated as an “abnormal immune response to ‘self’.” But such a simple statement belies the many theories that abound as to the cause and true pathogenesis of this disease category. Currently, as we have discussed above in our female versus male “autoimmune disease contest,” the exact cause of autoimmune disease is unknown. One theory is that some microorganisms (such as bacteria or viruses) or drugs may trigger changes that confuse the immune system. This may happen more often in people who have genes that make them more prone to autoimmune diseases [13]. But a new concept being promoted now (also genetically related, but poorly understood) is the “rogue B cell” and epitope spreading. This is another subject I'll ask your indulgence on because of its complexity, but it is an absolute “must” for understanding autoimmune disease. I personally believe it to be one of the strongest theories on autoimmune disease etiologies (along with XCI), but you'll have to decide that for yourself.

Back in Chapter 1, I urged you to fully understand the concept of the antigen presenting cell (APC) because of its continuing participation in both the innate and the adaptive immune response. I also made somewhat of a big deal over the T and B cells, the “infantry and special forces” as I called them of both innate and adaptive responses. And I think you will agree by now that my urging was fairly accurate given all we've discussed about the roles of T and B cells up to this point. Now, I'll need your heightened attention as we take their functions to a new level, not necessarily a good one either. (Perhaps we should record this as yet

another paradox.)

You'll recall that the T_H cells form APCs and activate B cells that are responsible for antibody production in response to an antigen. Antigens have small sites on their surfaces called epitopes or “antigenic determinants” that bind to a genetically predetermined corresponding receptor on the surface of the B cell (from our “antibody-encoding gene” discussion in Chapter 1, page 16). These B-cell receptors and epitopes are programmed genetically through the major histocompatibility complex (MHC—see page 11) on the T cells (specifically, T_H MHC Class 2 CD4 and MHC Class 1 T_C CD8) again, as described in Chapter 3. When toll-like receptors (TLRs or the “sentry cells”) signal MHCs that they have identified an infectious agent (i.e., bacteria and viruses) or tumorigenic antigens (carcinogens), the B cells undergo changes in their genes to produce antibodies that create strong attachments to the antigens' epitopes. (Every time I think about that process, I'm amazed!) This reaction also produces plasma cells that proceed to produce large amounts of antibodies. (Please don't quit on me now. I promise you, there's a pony in here and I'm getting to it.).

During this rapid proliferation and dispersion (or “spreading”) of antibodies from plasma cells, some B cells become “confused” (genetically altered) and begin to mistakenly interpret “self” as antigenic. This results in B-cells binding with “self” (yep, “you”) at local and distant sites. These autoantibody B cells are called “rogue B cells” and their migration is called “epitope spreading [14].” This spreading is what produces the clinical picture of the many autoimmune diseases whose signs and symptoms “spread” insidiously (Machiavellian-like) or gradually over time, from one organ to another, as well as among immune cells themselves. This spreading effect produces the diverse array of autoimmune diseases (e.g., from rheumatoid arthritis [RA] to Crohn's disease to kidney disease and on and on) and from one tissue type to another (e.g., from psoriatic skin disorders or nerve damaging multiple sclerosis [MS]) [15]. As you probably know, hopefully not directly, but through an unfortunate friend with an autoimmune disease that they usually suffer multiple autoimmune ailments.

It is theorized that this “rogue B-cell—epitope spreading” phenomenon is a product of dual genetic influences (messages) to the immune system. One influence occurs when genetic messages, along with other immune-stimulating factors (Chapter 4, page 72) tell the immune system to attack. Meanwhile, other beneficial messages (probably from Treg, T_C cells, apoptosis, neural downregulation, etc.) silence the immune system and try to stop it from dysregulating [16]. As you will see in the discussion on immunotherapies, both of these signals can be harnessed (to immunomodulate or immunosuppress) in treatments (especially in cancers). If the genetic influence is producing an autoimmune stimulus to attack (self), certain drugs like topoisomerase inhibitors (antimetabolites that suppress DNA synthesis) may prove valuable. Conversely, if the genetic influence is silencing the immune system (reducing the

autoantigenic effects, i.e., “a friend”) stimulating the system with proinflammatory biologics might be beneficial. And voilà –the pony! Needless to say, in this paradox, a very delicate balancing act is required [17].

You can see from this description that “rogue B cells” and epitope spreading have dramatic, negative potential for producing autoimmune diseases. However, you should also appreciate that understanding and scientifically manipulating this associated plasma cell antibody production and epitope spreading has the potential for enormously positives effects such as vaccine production. Also, another potential benefit from this phenomenon, under intense investigation, is to immunologically manipulate and regulate this rogue B cell, epitope spreading process in cancer therapies as mentioned above in the genetic messaging. Finally, during the early 2022 proofreading portion of this book, there was a new report on rogue B cells being implicated in advanced COVID-19 infections. We'll address this interesting late development in Chapter 7 on COVID-19.

3.6. The microbiome

One more quick visit to “the second genome,” the microbiome. While a new area of biomedical research, the microbiome has found a place in the theories of almost all human pathogenesis (not unlike the theory of chronic inflammation as the basis of *all* disease). And indeed, as we described in Chapter 3 (page 60), “… the constant 24/7 exposure of gut microbes to immune cells, from birth on, creates a chronic (even-if subclinical most of the time) inflammatory condition in all human biological systems.” Thus, the microbiome in an unrelenting effort to control chronic inflammation becomes a mitigating force against chronic inflammation, autoimmune disease, even cancers as it modulates the immune system. This function is illustrated in the potential etiologies of autoimmune diseases.

Conversely (just to confuse the whole picture just a bit further—like we need that, right?), dysbiosis (that imbalance in gut microbiome) is another important environmental factor that has been linked to the onset of different autoimmune diseases. The “gut microbiota—innate immunity axis” and symbiotic bacteria (short-chain fatty acids or SFCA) upregulate IL-6, IL-12, IFN, and TNF and further contribute to the pathogenesis of autoimmune diseases. Finally, epigenetic modulation (see Chapter 3) from SCFA metabolic by-products and interactions between gut microbiota and the innate immune system disrupt homeostasis and also contribute to the pathogenic process of autoimmune diseases [18]. To wit, recent studies have produced results confirming the effectiveness of probiotics in human nutrition by modulating SCFA production by the intestinal microbiome [19]. But the “gut microbiota—innate immunity axis” and symbiotic bacteria are only a small part of the microbiome's influence on pathogenicity. So let's not get too excited about probiotics quite yet.

4. Classification of autoimmune diseases

As presented in Chapter 4, the effects of chronic inflammation are profound and broadly deleterious to tissues and organ systems throughout the body. A principal reason for this diffuse pathological process is the affect chronic inflammation has on the network of blood vessels (particularly their adventitia and endothelial lining of their walls—called perivasculitis) that supply all of the bodily tissues and organs (see Chapter 4, Fig. 4.2). Whereas, the underlying cause of the disease process is in effect chronic inflammation, the clinical manifestations present themselves as specific tissue and organ system diseases (secondary to the chronic inflammation—Fig. 4.2, Chapter 4). These pathological effects manifest themselves in the form of clinical entities categorized as the autoimmune diseases.

As mentioned above in our description of epitope spreading, it is more than likely that this phenomenon contributes to the nature of autoimmune diseases as being specific to a bodily organ or tissue, and conversely being distributed, diffusely among multiple organ systems or tissues throughout the body. This “rogue B-cell” effect combined with the pervasive focal and diffuse vascular effects of chronic inflammation produces the multisystem organ/tissue-specific clinical manifestations (also diagnosed as multisystem inflammation syndrome in children or MIS-C) [19a] or the diffuse clinical picture synonymous with autoimmune diseases (Table 5.3). When considering the multiple theories of the pathogenesis of autoimmune diseases, it is apparent that there are, in fact, numerous causes (persistent antigens, environmental, autoantigens, etc.) beyond strictly the vascular and epitope spreading components we describe. However, as posited throughout this discussion, we come back to the ultimate predicate that the adaptive immune response leads to chronic inflammation, that ultimately leads to all autoimmune diseases.

In summary, to restate once more because of its clinical importance, by virtue of their etiologies (vascular and epitope spreading, and others no doubt), their pathology (chronic inflammation), and their immunologic molecular biology (cells, cytokines, proteins, etc.), the clinical presentations of autoimmune diseases can be classified as being associated with specific tissue(s) or organ system alone (e.g., psoriasis or Crohn's disease); or associated with multisystem organs and tissues simultaneously (e.g., RA or systemic lupus erythematosus [SLE]). It should also be noted that multiple autoimmune diseases, organ specific and/or diffuse, can occur simultaneously in the same patient (talk about an even more confusing diagnosis?) making the diagnosis of autoimmune diseases infinitely more difficult [20].

Table 5.3

Autoimmune Disease	Diffuse	Organ or tissue specific	Body system or tissue effected

Autoimmune Disease (alphabetical)	Diffuse	Organ or tissue specific	Body system or tissue effected
Alopecia areata	✓		Hair follicles, patchy hair loss
Ankylosing spondylitis		✓	Vertebral and sacro-iliac joints.
Antiphospholipid	✓		Increased blood clotting
Autoimmune hepatitis		✓	Liver inflammation
Behcet's syndrome		✓	Blood vessel inflammation (mouth)
Celiac disease		✓	Small intestines disease
Crohn's disease		✓	Entire gastrointestinal tract
Dermatomyositis		✓	Dermatological disease
Giant cell arteritis	✓		Diffuse vascular inflammation
Granulomatosis w polyangiitis	✓		Diffuse vascular inflammation
Graves' disease		✓	Thyroid gland disease
Guillain-Barre syndrome (GB	✓		Peripheral nerve involvement

Table Continued

Classification of autoimmune diseases by clinical presentation.

Autoimmune Disease (alphabetical)	Diffuse	Organ or tissue specific	Body system or tissue effected
Hashimoto's disease		✓	Thyroid gland disease
Hemolytic anemia			Red blood cells destroyed

		✓	
Idiopathic thrombocytope purpura	✓		Blood clotting inability
Inflammatory bowel disease (IBD)		✓	Inflammation of the colon
Juvenile rheumat arthritis (JRA)	✓		Joint inflammation in children
Mixed connective tissue disease	✓		Variable signs throughout body
Multiple sclerosis		✓	Brain and spinal cord (CNS)
Myasthenia gravis		✓	CNS and neuromuscular junction
Polyarteritis nodo	✓		Necrotizing vasculitis
Polymyalgia rheumatica	✓		Muscle pain esp. Shoulders/hips
Polymyositis	✓		Inflammatory myopathy (muscles)
Primary biliary cirrhosis		✓	Destruction of bile ducts

Table Continued

Autoimmune Disease (alphabetical)	**Diffuse**	**Organ or tissue specific**	**Body system or tissue effected**
Psoriasis		✓	Dermatological disease
Raynaud's phenomenon		✓	Decreased blood flow to fingers
Reactive arthritis	✓		Joint disorders caused by infection

Rheumatoid arthritis (RA)	✓		Diffuse inflammation of joints
Scleroderma		✓	Disease of skin and connective tissue
Sjogren's syndrome		✓	Disease of mucocutaneous tissue
Systemic lupus erythematosus (SLA)	✓		Involvement of all organs/tissues
Takayasu arteritis		✓	Inflammation of heart and aorta
Temporal arteritis		✓	Inflammation of temporal artery
Type 1 diabetes		✓	No insulin from pancreas
Ulcerative colitis		✓	Inflammation of colon
Vasculitis	✓		Inflammation of blood vessels
Vitiligo	✓		Loss of skin pigmentation

5. General clinical considerations with autoimmune diseases [21]

Throughout our discussions of specific autoimmune disease entities, you will recognize common denominators in their diagnosis and treatments (as mentioned previously in Chapter 4, page 86 on “nonspecific” drug therapies in chronic inflammation). What will change for each disease are the clinical manifestations (phenotypes) of the individual disease classifications based on cellular, tissue, and organ system(s) involved.

A person's genes are what “predispose” them or provide genetic susceptibility to dysregulate the immune system (e.g., “rogue B cell—epitope spreading), which in turn yields chronic inflammation and, in effect, creates the pathological damage to cells, tissues, and organ systems

synonymous with autoimmune diseases (there's yet another “bouncing ball” process for you. Yes, I know. Getting old). The environmental factors mentioned previously (e.g., smoking, pollution) along with the inherited alleles that an individual possesses for a specific gene (the genotype), combine to produce the “phenotype trigger” and the clinical manifestations of the disease state. This genetic approach to disease has led to the concept of “precision medicine” [22] (described in Chapter 3 and discussed throughout Section 2 of this book).

5.1. General signs and symptoms

Beyond signs and symptoms associated with chronic inflammation (presented in Chapter 4), below is a listing of the nonspecific symptoms most associated with autoimmune disease:

- Fatigue;
- Achy muscles;
- Swelling and redness;
- Low-grade fever;
- Trouble concentrating;
- Numbness and tingling in the hands and feet;
- Hair loss;
- Skin rashes.
- Body pain;
- Fever (often diagnostically referred to as “fever of unknown origin” or FUO);
- Constant fatigue and insomnia;
- Depression, anxiety and mood disorders;
- Gastrointestinal complications like constipation, diarrhea, and acid reflux;
- Weight gain;
- Frequent infections.

5.2. Diagnosis of autoimmune disease

The diagnosis of autoimmune disease can be challenging for two reasons. First, many of the associated diseases share similar symptoms. Second, as described previously, the disease process may be organ-specific or disseminated among multiple body systems. The diagnostic evaluation includes a thorough history, physical examination, laboratory testing, and imaging based on suspected tissue or organ-system involvement(s). Any additional tests mentioned in the diagnosis of chronic inflammation in Chapter 4 (page 84) should be considered part of an autoimmune disease evaluation as well.

5.2.1. Physical examination

In autoimmune diseases, signs and symptoms can vary considerably. As opposed to acute inflammation, chronic inflammation in autoimmune diseases can be difficult to identify without a history of precipitating acute inflammation. A chronically ill patient (chronic disease patient) can be assumed to have chronic inflammation as well. (To state it once again, " … chronic inflammatory disease is the progenitor or originating cause of *all* the major human disease categories.") [23].

In the case of immunosuppression or immunocompromised disease conditions, the symptoms are usually indirect as in increased illnesses, risk of infection, blood disorders, digestive problems, and delayed growth and development [24]. Regarding the array of autoimmune diseases, there have been more than 80 identified and affecting more than 50 million Americans (according to the American Autoimmune Disease Related Association, AARDA, 2019), 75% of whom are women [25] (for clarity, the 78% figure in the beginning of this chapter is an older 1997 US statistic which might suggest a "slight" improvement in the prevalence in women). Relative to the specific conditions, symptoms range from no symptoms at all to general malaise to severe illness and risk of death (similar to COVID-19 patients, particularly with obesity) [26].

5.2.2. Laboratory

No single laboratory test can diagnose autoimmune diseases. It requires a physical examination to assess signs and symptoms with a combination of lab tests. Antinuclear antibody (ANA) test identify antibodies that can bind to a normal cell nucleus. Their assessment in a blood test is often one of the first tests used when symptoms suggest an autoimmune disease. A positive ANA test indicates the potential presence of autoimmune disease (specific for SLE), but it does not confirm exactly which one, or even if one is present for certain. Alternate tests look for specific autoantibodies produced in certain autoimmune diseases. The bottom line in laboratory diagnosis is nonspecific and can only assist in the symptoms with other tests necessary to confirm the diagnosis [27].

5.2.3. Imaging

Based on a tentative diagnosis of an autoimmune disease, there is a likelihood that tissue(s) and organ(s) associated with the specific disease will demonstrate identifiable pathology. Examples include autoimmune respiratory diseases that will show distinct changes in lung X-rays; gastrointestinal related diseases will demonstrate distinct changes in endoscopic examinations; MS will reveal certain cerebral changes (e.g., calcifications on MRI scans). The combination of positive laboratory and imaging diagnostic indicators is all contributory, but only in combination with a careful physical assessment and patient history.

6. "Top 10" autoimmune diseases (clinical

descriptions, diagnosis, and treatment options) [28,29]

Now, let's present some specific descriptions of the “top 10” autoimmune diseases that we identify in Table 5.5. For each of the diseases, we will include a brief description of their etiologies; clinical signs and symptoms; diagnostic criteria; and finally, a listing of their treatments, including the immunotherapeutic agents (with their generic and brand names) used in their treatment. But please understand that therapeutic agents are being developed, FDA approved, and marketed on almost a monthly basis. As such, there will be additional drugs developed after the publication of this book that are not included. Details on any FDA approved (or experimental) drugs you might be familiar with that are not listed in Table 5.4 should be available in the online literature. Also, after this section we will revisit, in greater depth, pharmacology and pharmacodynamics of the immunotherapies mentioned in the treatment options for each of these top 10 autoimmune diseases.

First, I would refer you back to Table 5.1 that lists some of the diseases (38 of a total of about 80) associated with the autoimmune response where you can begin to see the magnitude of this pathological category. To further emphasize the extent and thus, the prevalence of autoimmune diseases (approximately 8% of the general population [30]), Table 5.5 lists the top 10 autoimmune diseases. I'm sure you will recognize and note the “popularity” of each of these diseases in today's world.

Now, as promised, I will present a brief clinical description, diagnostic considerations and a listing of treatment options for each of the “top 10.” And, please remember, in the interest of “saving trees”, I will not be revisiting the immunological characteristics (molecular biology and immunopathophysiology) for each of these autoimmune diseases. Rather, simply remember that they all, directly and indirectly, share the same immunology, chronic inflammatory mechanisms, molecular biology, and genetics that we have been describing and discussing up to this point throughout this book. Also, a large percentage of the immunotherapeutic agents under each of the “Treatment” sections in this “top 10” listing include medications (generic and brand names) used for multiple disease categories (i.e., nonspecific therapies as described throughout Chapters 4 and 5).

Table 5.4

Brand name	Mechanism
Orencia	T-cell inhibitor
Humira	TNF inhibitor
Actemra	TNF inhibitor
Azasan	Purine synthesis inhibitor
Plaquenil	Suppression of IL-1 & TNF-α, induce apoptosis of inflammation cells &

	decrease chemotaxis
Sandimmune	Calcineurin inhibitor
Enbrel	TNF inhibitor
Simponi	TNF inhibitor
Remicade	TNF inhibitor
Arava	Pyrimidine synthesis inhibitor
Trexall	Purine metabolism inhibitor
Minocin	5-LO inhibitor
Rituxan	Monoclonal antibody
Azulfidine	Suppression of IL-1 & TNF-α-

Examples of biologic immunopharmacotherapeutics.

Source: Louis J. Catania © 2022.

Table 5.5

1. Rheumatoid arthritis
2. Systemic lupus erythematosus (SLE)
3. Inflammatory bowel disease (IBD)
4. Crohn's Disease
5. Multiple sclerosis (MS)
6. Type 1 diabetes mellitus
7. Guillain-Barre syndrome
8. Psoriasis
9. Graves' disease
10. Myasthenia gravis

Ten (10) most common autoimmune diseases.

Source: Foundations of AI in Healthcare and Bioscience; Catania; Academy Press. November 2020.

6.1. Rheumatoid arthritis (RA)

Description: This is a relatively common (over 25 million effected), long-term condition that primarily affects joints. It typically results in warm, swollen, and painful joints, most commonly, the wrist and hands, as well as multiple joints (polyarthritis) with the same joints typically involved on both sides of the body. Symptoms present mostly in the morning on waking or following prolonged inactivity. The disease may also affect other parts of the body (i.e., multisystem) including inflammation around the lungs and heart, cardiovascular disease, osteoporosis, interstitial lung disease, infection, cancer, and vasculitis in long-term disease. Often,

symptoms come on gradually over weeks to months. The cause of RA is believed to involve a combination of genetic and environmental factors. The diagnosis is made mostly on the basis of a person's signs and symptoms.

Diagnosis:

- Difficult to diagnose in its early stages because early signs and symptoms mimic those of many other diseases;
- Elevated erythrocyte sedimentation rate (ESR, or sed rate);
- C-reactive protein (CRP) that may indicate the presence of an inflammatory process in the body;
- Rheumatoid factor and anticyclic citrullinated peptide (anti-CCP) antibodies;
- No one blood test or physical finding confirms the diagnosis.
- Laboratory testing:
    - Blood tests:
        - Erythrocyte sedimentation rate (ESR, or sed rate);
        - C-reactive protein (CRP),
        - Rheumatoid factor;
        - Anticyclic citrullinated peptide (anti-CCP) antibodies.
    - Imaging test

Treatment:

- Nonsteroidal antiinflammatory drugs (NSAIDs):
    - Over-the-counter NSAIDs;
    - Stronger NSAIDs are available by prescription;
    - Side effects may include stomach irritation, heart problems and kidney damage.
- Corticosteroid medications:
    - Prednisone;
    - Methylprednisolone (Medrol)
    - Dexamethasone;
    - Side effects may include thinning of bones, weight gain and diabetes.
- Disease-modifying antirheumatic drugs (DMARDs):
    - Methotrexate (Trexall, Otrexup, others);
    - Leflunomide (Arava);

- ○ Hydroxychloroquine (Plaquenil);
- ○ Sulfasalazine (Azulfidine);
- ○ Side effects vary but may include liver damage, bone marrow suppression, and severe lung infections.

• Biologic agents (newer class of DMARDs):

- ○ Abatacept (Orencia);
- ○ Adalimumab (Humira);
- ○ Anakinra (Kineret);
- ○ Baricitinib (Olumiant);
- ○ Certolizumab (Cimzia);
- ○ Etanercept (Enbrel);
- ○ Golimumab (Simponi);
- ○ Infliximab (Remicade);
- ○ Rituximab (Rituxan);
- ○ Sarilumab (Kevzara);
- ○ Tocilizumab (Actemra);
- ○ Tofacitinib (Xeljanz);
- ○ Biologic drugs increase the risk of infections;
- ○ Higher doses of Tofacitinib can increase the risk of blood clots in the lungs;
- ○ Biologic (DMARDs) are usually most effective when paired with a nonbiologic DMARD, such as methotrexate.

• Surgery

- ○ Synovectomy: Surgery to remove the inflamed lining of the joint (synovium) can be performed on knees, elbows, wrists, fingers, and hips;
- ○ Tendon repair: Inflammation and joint damage may cause tendons around your joint to loosen or rupture. Your surgeon may be able to repair the tendons around your joint;
- ○ Joint fusion: Surgically fusing a joint may be recommended to stabilize or realign a joint and for pain relief when a joint replacement isn't an option;

- ○ Total joint replacement: During joint replacement surgery, your surgeon removes the damaged parts of your joint and inserts a prosthesis made of metal and plastic;

6.2. Systemic lupus erythematosus (SLE)

Description: This is the quintessential, multisystem, diffuse autoimmune disease attacking healthy tissue and organ systems in many parts of the body. It is known as “the great imitator” (also an idiom for syphilis but no

actual or implied association with SLE) because it often mimics or is mistaken for so many other illnesses. Symptoms vary from mild to severe including painful and swollen joints (less severe than RA), fever, chest pain, mouth ulcers, swollen lymph nodes, feeling tired, and a red rash (up to 70%) that is more common on the face. Cardiovascular complications include perivasculitis, myocarditis and endocarditis, and mitral valve or tricuspid valve involvement. There is a pattern of periods of illness (flares), and periods of remission with few symptoms. Women of childbearing age are affected about nine times more often than men. (Theories on reasons for this strong gender predilection are covered on page 95.) While it is considered a hereditary disorder that most commonly begins between the ages of 15 and 45, a wide range of ages are affected. The immunopathology involves an adaptive immune response by autoantibodies, most commonly antinuclear antibodies that are the strongest diagnostic sign of the disease. Life expectancy is lower among SLE patients due to the significant increased risk of cardiovascular disease, with that being the most common cause of death.

Diagnosis: (Really “classification” vs. diagnosis: where four or more criteria are required):

- Malar rash;
- Discoid rash;
- Photosensitivity (development of a rash after sun exposure);
- Oral or nasal ulcers; arthritis of multiple joints; serositis (inflammation of the lining around the lungs or heart);
- Kidney disease indicated by protein or casts in the urine;
- Neurological disorders such as seizures and psychosis;
- Blood disorders such as hemolytic anemia, leukopenia, and lymphopenia;
- Hair loss or breaking, especially around the forehead; and
- Raynaud's Phenomenon, a two- or three-color change of the fingertips upon cold exposure.
- Diagnostic testing:

    ○ Laboratory tests

- Complete blood count (CBC);
- Erythrocyte sedimentation rate (ESR);
- Kidney and liver assessment;

- Urinalysis;
- Antinuclear antibody (ANA) test.

    ○ Imaging tests

- Chest X-ray;
- Echocardiogram.

- Biopsy

Treatment

- Nonsteroidal antiinflammatory drugs (NSAIDs):
  - Over-the-counter NSAIDs;
  - Stronger NSAIDs are available by prescription;
  - Side effects may include stomach irritation, heart problems and kidney damage.
- Antimalarial drugs:
  - Hydroxychloroquine (Plaquenil);
- Corticosteroids;
  - Prednisone;
  - Methylprednisolone (Medrol);
  - Dexamethasone.
- Immunosuppressants.
  - Azathioprine (Imuran, Azasan);
  - Mycophenolate (Cellcept);
  - Methotrexate (Trexall, Xatmep, others);
  - Cyclosporine (Sandimmune, Neoral, Gengraf);
  - Leflunomide (Arava).
- Biologics:
  - Belimumab (Benlysta) administered intravenously;
  - Rituximab (Rituxan, Truxima).

6.3. Inflammatory bowel disease (IBD)

Description: This is a group of autoimmune inflammatory conditions of the colon and small intestine, thus an organ specific disease. It includes ulcerative colitis (UC) and, in some classifications, Crohn's disease (below). Symptoms include abdominal pain, diarrhea, rectal bleeding, severe internal cramps/muscle spasms in the region of the pelvis and weight loss. The diagnosis is generally made by assessment of inflammatory biomarkers in the stool followed by colonoscopy with biopsy for pathological lesions (also associated with UC). Etiology is believed to be interaction of environmental and genetic factors leading to immunological responses and inflammation in the intestine. Microbial symbiosis and immune factors produce alterations in the gut microbiome contributing to inflammatory gut diseases. IBD-affected individuals have been found to have 30%–50% reduced biodiversity of commensal bacteria in their gut. A

genetic component to IBD has been clearly recognized for years through research and genetic sequencing of ethnic groups (e.g., Ashkenazi Jews), familial clustering, epidemiological studies, and twin studies.

Diagnosis:

Laboratory tests:

- Tests for anemia or infection;
- Stool studies;

Endoscopy:

- Colonoscopy;
- Flexible sigmoidoscopy;
- Upper endoscopy;
- Capsule endoscopy;
- Balloon-assisted enteroscopy.

Imaging procedures:

- X-ray;
- Computerized tomography (CT) scan;
- CT enterography (provides better images of the small bowel);
- Barium X-rays;
- Capsule endoscopy;
- Magnetic resonance imaging (MRI).

Treatment:

Antiinflammatory drugs:

- Corticosteroids;
- Aminosalicylates, such as mesalamine (Asacol HD, Delzicol, others);
- Balsalazide (Colazal);
- Olsalazine (Dipentum).

Immunosuppressants:

- Azathioprine (Azasan, Imuran);
- Mercaptopurine (Purinethol, Purixan);
- Methotrexate (Trexall).

Biologics:

- Infliximab (Remicade);
- Adalimumab (Humira);
- Golimumab (Simponi);
- Certolizumab (Cimzia);

- Vedolizumab (Entyvio);
- Ustekinumab (Stelara).

Antibiotics:

- Ciprofloxacin (Cipro);
- Metronidazole (Flagyl).

Antidiarrheal medications.
Pain relievers.
Vitamins and supplements.
Nutritional support.
Surgery.

6.4. Crohn's disease (CD)

Description: This is a type of inflammatory bowel disease (IBD) with the most prominent distinction being its effect on any segment of the gastrointestinal tract from the mouth to the anus. Considering that all those structures and tissues are part of the gastrointestinal tract, Crohn's is considered an organ-specific disease although it is known to produce anemia, skin rashes, arthritis, inflammation of the eye, and fatigue. Its etiology includes a combination of environmental, immune, and bacterial factors in genetically susceptible individuals (more than 70 genes having been found to be involved). Abdominal pain is the hallmark initial symptom of Crohn's disease, especially in the lower right abdomen. It is often accompanied by diarrhea, that may or may not be bloody. Flatulence, bloating, and abdominal distension are additional symptoms and add to the intestinal discomfort. As with other autoimmune diseases, there is no cure for Crohn's but increasing amounts of immunotherapeutics are showing promise (discussed below). Males and females are equally affected and the rate of the disease seems to be increasing since 1970. Many people with Crohn's disease have symptoms for years before the diagnosis. The usual onset is in the teens and twenties, but can occur at any age. People with Crohn's disease experience chronic recurring periods of flare-ups and remission. Crohn's disease seems to be due to a combination of environmental factors and genetic predisposition. It is the first genetically complex disease in which the relationship between genetic risk factors and the immune system is understood in considerable detail. Some new research is suggesting that this autoimmune disease may be associated more directly with the innate versus the adaptive immune system through impaired cytokine secretion by macrophages and/or an overactive T_H function.

Diagnosis: Same as inflammatory bowel disease (IBD).

Treatment: Same as inflammatory bowel disease (IBD).

6.5. Multiple sclerosis (MS)

Description: Also known as encephalomyelitis disseminata, MS is a demyelinating disease in which the insulating covers of nerve cells in the brain and spinal cord are damaged, disrupting the ability of parts of the nervous system to transmit signals. The results are physical, mental, and sometimes psychiatric problems with specific symptoms to include almost any neurological symptom or sign, with autonomic, motor, sensory problems and particularly vision signs, most common being double vision, blurring and blindness in one eye (secondary to optic neuritis), muscle weakness and trouble with sensation or coordination. In that MS can affect nerves in any part of the body and the organs they innervate, we can consider it a diffuse, multisystem disorder (including in children as multisystem inflammation syndrome in children or MIS-C) [30a]. The course of symptoms occurs in two main patterns initially: either as episodes of sudden worsening that last a few days to months (called relapses, exacerbations, bouts, attacks, or flare-ups) followed by improvement (85% of cases) or as a gradual worsening over time without periods of recovery (10%–15% of cases). The cause of MS is unknown, but some combination of genetic and environmental factors such as infectious agents is suspected. It has an odd distribution with a strong prevalence in northern European countries and other worldwide geographic pockets with no incidence at all. This phenomenon may relate to the postulated infectious agent (e.g., virus) etiology.

Diagnosis:

- Blood tests;
- Spinal tap (lumbar puncture);
- MRI;
- Evoked potential tests.

Treatment:

- Corticosteroids:
  - Oral prednisone;
  - Intravenous methylprednisolone.
- Plasma exchange (plasmapheresis)
- Injectable treatments include
  - Interferon beta medications;
  - Glatiramer acetate (Copaxone, Glatopa).
- Oral treatments:

- ○ Fingolimod (Gilenya);
- ○ Dimethyl fumarate (Tecfidera);
- ○ Diroximel fumarate (Vumerity);

- ○ Teriflunomide (Aubagio);
- ○ Siponimod (Mayzent);
- ○ Cladribine (Mavenclad).

6.6. Type 1 diabetes [31]

Description: Previously known as juvenile diabetes, Type 1 diabetes is a form of diabetes in which very little or no insulin is produced by the islets of Langerhans in the pancreas. It makes up an estimated 5%–10% of all diabetes cases and typically begins in children and young adults. Insulin is a hormone required for the body to use blood sugar and thus its absence or reduction produces high blood sugar levels. It is believed to involve a combination of over 50 genes and environmental factors and its underlying mechanism involves an autoimmune destruction of the insulin producing beta cells in the pancreas. The classic symptoms of Type 1 diabetes include polyuria (increased urination), polydipsia (increased thirst), dry mouth, polyphagia (increased hunger), fatigue, and weight loss. It is often diagnosed when diabetic ketoacidosis occurs (rapid deep breathing, drowsiness, increased thirst, frequent urination, abdominal pain, and vomiting).

Diagnosis:

- Fasting plasma glucose level at or above 7.0mmol/L (126mg/dL);
- Symptoms of hyperglycemia and casual plasma glucose at or above 11.1mmol/L (200mg/dL);
- Glycated hemoglobin (hemoglobin A1C) at or above 48mmol/mol (≥6.5 DCCT %);
- Appearance of diabetes-related autoantibodies.

Treatment:

- Taking insulin (lifelong requirement);
- Carbohydrate, fat, and protein counting;
- Frequent blood sugar monitoring;
- Eating healthy foods;
- Exercising regularly and maintaining a healthy weight;

Medications:

- High blood pressure medications:
  - ○ Angiotensin-converting enzyme (ACE) inhibitors;
  - ○ Angiotensin II receptor blockers (ARBs);

- Aspirin;
- Cholesterol-lowering drugs with the following therapeutic criteria:
    - Low-density lipoprotein (LDL, or “bad”) cholesterol be below 100mg/dL (2.6mmol/L);
    - High-density lipoprotein (HDL, or “good”) cholesterol is recommended to be over 50mg/dL (1.3mmol/L) in women and over 40mg/dL (1mmol/L) in men;
    - Triglycerides, another type of blood fat, ideal when they're less than 150mg/dL (1.7mmol/L).
- Blood sugar monitoring
- Healthy eating and monitoring carbohydrates
    - Fruits
    - Vegetables
    - Whole grains
- Physical activity
- Potential future treatments
    - Pancreas transplant;
    - Islet stem cell transplantation (see Section 8.1 below).

6.7. Guillain-Barre syndrome (GBS)

Description: The immune system attacks the peripheral nervous system, the network of nerves located outside of the brain and spinal cord. It can range from a very mild case with brief weakness to nearly devastating paralysis, leaving the person unable to breathe independently. Fortunately, most people eventually recover from even the most severe cases of GBS. After recovery, some people will continue to have some degree of weakness. Unexplained sensations often occur first, such as tingling in the feet or hands, or even pain (especially in children), often starting in the legs or back. These sensations tend to disappear before the major, longer-term symptoms appear. Symptoms often affect the arms, breathing muscles, and even the face, reflecting more widespread nerve damage. Most people reach the greatest stage of weakness within the first 2weeks after symptoms appear; by the third week 90% of affected individuals are at their weakest.

Diagnosis:

- Symptoms appear rapidly on both sides of the body (the typical finding in Guillain-Barré syndrome) and the speed with which the symptoms appear
- Deep tendon reflexes in the legs, such as knee jerks, are usually

lost;
- Reflexes may also be absent in the arms;
- Spinal tap (lumbar puncture) produces cerebrospinal fluid with more protein than usual but very few immune cells.

Treatment:

- Plasma exchange (plasmapheresis);
- Immunoglobulin therapy.

6.8. Psoriasis

Description: Skin disorder that causes skin cells to multiply up to 10 times faster than normal. This makes the skin build up into bumpy red patches covered with white scales. It is not contagious. It usually appears in early adulthood and generally affects just a few areas. In severe cases, psoriasis can cover large parts of the body. The patches can heal and then come back throughout a person's life. Some common symptoms for plaque psoriasis, the most common form, include red skin, often covered with silver-colored scales. The plaques may be itchy and painful, and they sometimes crack and bleed. In severe cases, the plaques will grow and merge, covering large areas. Common sites include plaques of scales or crust on the scalp, fingernails and toenails, including discoloration and pitting of the nails and may also crumble or detach from the nail bed. Patients with psoriasis can also get a type of arthritis called psoriatic arthritis with pain and swelling in the joints. The condition is an unknown autoimmune disease with a tendency to be a familial trait, although it may skip generations.

Diagnosis:

- History and physical examination of the plaques.

Treatment:
Topical therapy (creams and ointments):

- Corticosteroids:
  - Hydrocortisone
  - Triamcinolone (Acetonide, Trianex);
  - Clobetasol (Temovate).
- Methotrexate:
  - (Trexall)
  - Adalimumab (Humira)

- Infliximab (Remicade).

- Cyclosporine.
- Biologics:
  - Etanercept (Enbrel);
  - Infliximab (Remicade);
  - Adalimumab (Humira);
  - Ustekinumab (Stelara);
  - Secukinumab (Cosentyx);
  - Ixekizumab (Taltz).

- Other medications:
  - Thioguanine (Tabloid);
  - Hydroxyurea (Droxia, Hydrea);
  - Apremilast (Otezla).

- Vitamin D analogues;
  - Calcipotriene;
  - Calcitriol (Vectical).

- Retinoids;
  - Tazarotene (Tazorac, Avage);
  - Acitretin (Soriatane).

- Calcineurin inhibitors;
  - Tacrolimus (Protopic);
  - Pimecrolimus (Elidel).

- Salicylic acid.
- Coal tar:
  - Goeckerman therapy. Coal tar treatment with UVB light therapy;
  - Anthralin.

- Light therapy
  - Sunlight.
  - UVB broadband.
  - UVB narrowband.
  - Psoralen plus ultraviolet A (PUVA).
  - Excimer laser. Oral or injected medications

- Alternative medicine:

○ Aloe extract cream;
○ Fish oil supplements;
○ Oregon grape;
○ Essential oils.

6.9. Graves' disease

Description: This is an immune system disorder that results in the overproduction of thyroid hormones (hyperthyroidism). It is the most common cause of hyperthyroidism. Thyroid hormones affect many body systems, so signs and symptoms of Graves' disease can be wide ranging. Although it may affect anyone, it's more common among women and in people younger than age 40. The antibody associated with Graves' disease, thyrotropin receptor antibody (TRAb), acts like the regulatory pituitary hormone. That means that TRAb overrides the normal regulation of the thyroid, causing an overproduction of thyroid hormones (hyperthyroidism).

Diagnosis:

- Anxiety and irritability;
- A fine tremor of the hands or fingers;
- Heat sensitivity and an increase in perspiration or warm, moist skin;
- Weight loss, despite normal eating habits;
- Enlargement of the thyroid gland (goiter);
- Change in menstrual cycles;

- Erectile dysfunction or reduced libido;
- Frequent bowel movements;
- Bulging eyes (Graves' ophthalmopathy—25% to 50%);
- Fatigue;
- Thick, red skin usually on the shins or tops of the feet (Graves' dermopathy);
- Rapid or irregular heartbeat (palpitations);
- Sleep disturbance.

Laboratory tests:

- Graves' Disease Blood Tests.
- Testing TSH Levels;
- Testing Total T3 and T4 Hormone Levels;
- Testing Free T4 Hormone Levels;
- Testing Thyroid Peroxidase Antibodies (TPO) Level;
- Radioactive Iodine Uptake (RAIU) and Scan;
- Ultrasound;
- Image testing.

Treatment:

- Radioactive iodine therapy;
- Antithyroid medications:
    - Propylthiouracil;
    - Methimazole (Tapazole).
- Beta blockers include
    - Propranolol (Inderal, InnoPran XL);
    - Atenolol (Tenormin);
    - Metoprolol (Lopressor, Toprol-XL);
    - Nadolol (Corgard).
- Surgery:
    - Thyroidectomy;
    - Subtotal thyroidectomy
- Treating Graves' ophthalmopathy
    - Teprotumumab (Tepezza);
    - Prisms (for double vision);
    - Orbital decompression surgery;
    - Orbital radiotherapy.

6.10. Myasthenia gravis (MG)

Description: This disease is characterized by weakness and rapid fatigue of any of the muscles under your voluntary control. It's caused by a breakdown in the normal communication between nerves and muscles. Symptoms include weakness of arm or leg muscles, double vision, drooping eyelids, and difficulties with speech, chewing, swallowing and breathing. Though the disease can affect people of any age, interestingly it's more common in women younger than 40 and in men older than 60. Symptoms tend to progress over time, usually reaching their worst within a few years after the onset of the disease.

Diagnosis:

Neurological examination:

- Reflexes;
- Muscle strength;
- Muscle tone;
- Senses of touch and sight;
- Coordination;
- Balance;
- Edrophonium test: Injection of the chemical edrophonium chloride that results in a sudden, temporary improvement in

muscle strength;
- Blood analysis;
- Repetitive nerve stimulation:
- Single-fiber electromyography (EMG);
- Imaging (CT scan and MRI);
- Pulmonary function tests.

Treatment:
Medications

- Cholinesterase inhibitors;
    - Pyridostigmine (Mestinon, Regonal);
    - Neostigmine (Bloxiverz).
- Corticosteroids;
- Immunosuppressants;
    - Azathioprine (Azasan, Imuran);
    - Mycophenolate mofetil (Cellcept);
    - Cyclosporine (Sandimmune);
    - Methotrexate (Trexall);
    - Tacrolimus (Astrograf XL, Prograf).
- Intravenous therapy:
    - Plasmapheresis;
    - Intravenous immunoglobulin (IVIg);
    - Monoclonal antibody:
    - Rituximab (Rituxan);
    - Eculizumab (Soliris).
- Surgery:
    - Video-assisted thymectomy;
    - Robot-assisted thymectomy.

7. General therapeutics considerations with autoimmune diseases

Now, let's discuss the pharmacology and pharmacodynamics of the immunotherapy drugs (most listed above under the specific conditions for which they are used) and immunotherapeutic procedures. As we have discussed and emphasized numerous times, chronic inflammation and

autoimmune diseases often require treatment directed at the tissue(s) and organ system(s) or more generalized treatment falling under the categories of immunosuppressive and immunomodulating (suppressing or stimulating) therapies, sometimes referred to as “nonspecific therapies.” Because of the parallel nature of chronic inflammation and autoimmune disease, as we have elaborated on in these previous 2 chapters, we included a listing of the therapeutic options in Table 5.4 (page 112). Now it's time to “go deeper” on their mechanisms and usage.

7.1. Immunotherapies

Some of the organ/tissue-specific treatments and procedures for autoimmune diseases are delivered as targeted strategies directed to the effected organs (e.g., antithyroid medications for Grave's disease) or tissues (e.g., topical corticosteroids for psoriasis). In the case of diffuse/multisystem autoimmune conditions (including diabetes and cancers), the more generalized treatments (the “non-specific therapies”) are classified as immunosuppressive and immunomodulating (suppressing or stimulating) therapies. These immunotherapeutics (i.e., pharmacologic immunomodulation) target the cellular, biochemical and molecular biological processes occurring in chronic inflammation as discussed in the section on pharmacodynamics in Chapter 4 (page 77). A comprehensive list of immunotherapeutic medication options (Table 5.6) includes most of the current drugs used for chronic inflammation, autoimmune diseases, and cancers.

Table 4.2 (back in Chapter 4, page 79) is a limited list of pharmacologic, proinflammatory mediators (and their actions) used to immunomodulate the mechanisms that drive the pharmacodynamics of chronic inflammation. The basis of medical therapies for autoimmune diseases (and again, chronic inflammation) to elicit desired therapeutic effects is the immunomodulation (amplifications, supplementation, suppression) of the chemical and molecular components identified in the right-hand column of Fig. 2.3. (I know I'm getting deeper as I warned would be the case in this section. But I promise to try to keep it “simple … but not simpler.”)

On the left side of Fig. 2.3 are the pharmacologic pathways, cyclooxygenase and lipoxygenase, most responsible for acute inflammation. The nonspecific drugs used for these pathways in acute inflammation include corticosteroids and NSAIDs (discussed in Chapter 2, page 36). These drugs are of some value in chronic inflammation and autoimmune diseases as well, where they suppress the immune system's molecular (cellular and humoral) biology. They rarely prove totally adequate for maximal therapy, although the corticosteroids do suppress advanced inflammatory damage as has been demonstrated (with dexamethasone) in their effectiveness for late stage COVID-19 (more in Chapter 7). Rather, the principal approach in treating chronic inflammation is obviously to suppress those immunochemical and

molecular biologic processes (right side of Fig. 2.3) that are promoting inflammatory (proinflammatory cytokine) changes and conversely, to stimulate and promote those agents that inhibit the inflammatory process (see Table 4.2 from Chapter 4, page 79).

Table 5.6

- Abatacept (Orencia)
- Adalimumab (Humira)
- Alemtuzumab (Campath)
- Anakinra (Kineret)
- Apremilast (Otezla)
- Atezolizumab (Tecentriq)
- Avelumab (Bavencio)
- Azathioprine (Azasan, Imuran)
- Basiliximab (Simulect)
- Belimumab (Benlysta)
- Belinostat (Beleodaq)
- Bevacizumab (Avastin)
- Brentuximab (Adcetris)
- Canakinumab (Ilaris)
- Certolizumab (Cimzia)
- Cetuximab (Erbitux)
- Cladribine (Mavenclad)
- Clofarabine (Clolar)
- Cobimetinib (Cotellic)
- Corticosteroids
- Cyclophosphamide (Cytoxan, Neosar)
- Cyclosporine (Sandimmune, Neoral, Gengral)
- Dacarbazine (DTIC-Dome)
- Daclizumab (Zinbryta)
- Dasatinib (Sprycel)
- Daunorubicin (Cerubidine)
- Decitabine (Dacogen)
- Denileukin diftitox (Ontak)
- Dexamethasone
- Dimethyl fumarate (Tecfidera)
- Diphenhydramine (Benadryl)
- Diphenoxylate/atropine (Lomotil)
- Doxorubicin (Adriamycin)
- Durvalumab (Imfinzi)
- Elotuzumab (Empliciti)
- Enzalutamide (Xtandi)
- Epirubicin (Ellence)
- Etanercept (Enbrel)
- Etoposide (Toposar, VePesid)
- Fingolimod (Gilenya)
- Gemtuzumab (Mylotarg)
- Glatiramer acetate (Copaxone, Glatopa).
- Golimumab (Simponi)
- Hydroxychloroquine (Plaquenil)
- Hydroxyurea (Droxia, Hydrea)
- Infliximab (Remicade)
- Ipilimumab (Yervoy)
- Ixekizumab (Taltz)

Immunotherapeutic medication options for chronic inflammation, autoimmune diseases and cancers (Generic and brand names/… mab suffix=monoclonal antibody).

7.2. Monoclonal antibodies [32]

(Please note here that additional discussions on monoclonal antibodies appear in Chapter 2, page 39; Chapter 5, page 128; Chapter 6, page 163;

and Chapter 7, page 200. I would say that this suggests the importance and potential value of monoclonal antibodies in immunologic diseases [and beyond].)

In some cases, immunotherapeutic drugs are used for multiple purposes and sometimes the actual cells and chemicals (humoral agents) involved in a bodily process are used to supplement the body's own defense mechanisms. As an example, monoclonal antibodies (any drug with the suffix, "… mab" in the generic name—list included as Table 5.7) are laboratory antibodies (or actual patients' antibodies) engineered and used to mimic the immune system's own antibody response to a specific antigen and its potential resultant chronic inflammation. These antibodies are made by identical immune cells that are all clones of a unique parent cell. Another example of cellular and humoral bodily agents used as immunotherapeutics include cocnvalescent plasma (to be discussed in Chapter 7).

Monoclonal antibodies, also referred to as biologics, are immune system proteins that are created in the lab. Antibodies are produced naturally by your body (cellular, humoral, antibodies, etc.) and help the immune system recognize germs that cause disease, such as bacteria and viruses, and mark them for destruction (all the processes from Chapters 1 and 2). Like your body's own antibodies, monoclonal antibodies recognize specific targets. They are often generated by isolating or transforming antibody-producing cells taken directly from immunized animals or patients, and transplanting the antibody-encoding genes (see Chapter 1, page 16) of these cells into suitable producer cell lines, rather than using hybridoma technology (method for producing large amounts of identical antibodies). Rather than wait for the body to make its own antibodies, scientists are studying versions of these molecules to directly disable the antigen.

Table 5.7

- **Adalimumab (Humira)**
- **Atezolizumab (Tecentriq)**
- **Avelumab (Bavencio)**
- **Belimumab (Benlysta)**
- **Bezlotoxumab (Zinplava)**
- **Cemiplimab (Libtayo)**
- **Certolizumab (Cimzia)**
- **Daratumumab (Darzalex)**
- **Eculizumab (Soliris)**
- **Golimumab (Simponi)**
- **Infliximab (Remicade)**
- **Ipilimumab (Yervoy)**
- **Ixekizumab (Taltz)**
- **Nivolumab (Opdivo)**
- **Obinutuzumab (Gazyva)**
- **Ofatumumab (Arzerra)**
- **Panitumumab (Vectibix)**
- **Pembrolizumab (Keytruda)**
- **Ramucirumab (Cyramza)**
- **Rituximab (Rituxan, Truxima)**
- **Secukinumab (Cosentyx)**
- **Tocilizumab (Actemra)**
- **Trastuzumab (Herceptin)**
- **Ustekinumab (Stelara)**
- **Vedolizumab (Entyvio)**

Monoclonal antibody options (generic and brand names).

Along with other outstanding researchers, Dr. Anthony Fauci identified antibodies on B cells that could make endless copies of itself. These "cloned" monoclonal antibodies could then be categorized by which antibodies responded to which antigens (pathogens, carcinogens, etc.).

From this information, drugs were designed with specific types of monoclonal antibodies that would attack an identified antigen. These drugs have become a dominant immunotherapeutic medical treatment for a vast number of diseases including the autoimmune diseases, cancers and COVID-19, all to be discussed further in Chapter 6 (cancers) and 7 (COVID-19). This accomplishment by Dr. Fauci and his team has changed the face of health care as monoclonal antibodies have revolutionized disease care in the 21st century and have become the successful therapy and drug of choice in early COVID-19 patients.

7.3. Biologics [33]

Beyond monoclonal antibody drugs, a second category of immunomodulating drugs, in the immunosuppressive category is a group termed " DMARDs," disease-modifying anti-rheumatic drugs [34]. These include such drugs as hydroxychloroquine (you've heard of that one, I'm sure!), methotrexate, sulfasalazine, and leflunomide. Second are the "biologic drugs" [35] (a generic term) that are a category attempting to regulate (increase or decrease) the immune response. These biologics are nonspecific (or generic) for the range of diseases produced from chronic inflammation and act on the immunopharmacology to biochemically inhibit proinflammatory agents or promote inhibitory agents (Table 5.7). Among these biologics are a large number of drug options (particularly the monoclonals) including Tocilizumab, Etanercept, Adalimumab, Abatacept, and many others presented in the discussions above on treatment of specific autoimmune diseases with their immunomodulating mechanisms.

Some more of the popular nonspecific immunotherapeutic agents include cytokines like interferons; interleukins; anti-TNFs (tumor necrosis factor [e.g., tocilizumab and abatacept], a strong proinflammatory cytokine that promotes apoptosis or cell-death, thus engendering malignant cell death and that of overly active immune cells); gene-based delivery systems; and other immune system modulators. Of course, as with corticosteroids and any immunosuppressive agents, the risk of secondary infection must always be considered (see the rationale for such risk in Chapter 2, page 36) and, if identified, must be treated with appropriate antibiotics. I specifically mention tocilizumab (Actemra) and abatacept (Orencia) above because this secondary infectious risk has been shown to be elevated in these TNF inhibitors. However, let's not "throw the baby out with the bathwater" (yes, I know, another trite saying), in that one of these monoclonal antibody TNF inhibitors, tocilizumab, is showing promise for cancer therapies while conversely, abatacept is getting some great reviews in the literature for effectiveness against COVID-19 and cancers.

Checkpoint inhibitors [36] are monoclonal antibody drugs that target and attach to PD-1, PD-L1, and CTLA-4 proteins on T cells (and some cancer cells). This binding action can inhibit the proteins and boost the immune response against cancer cells (more on this in Chapter 6 on

Cancer). These drugs are given intravenously and have been shown to be helpful in treating several types of cancers with new cancer types being added as more studies show the drugs to be effective. Examples of drugs that target PD-1 include Pembrolizumab (Keytruda), Nivolumab (Opdivo), and Cemiplimab (Libtayo). PD-L1 drugs include Atezolizumab (Tecentriq), Avelumab (Bavencio) and Durvalumab (Imfinzi). Ipilimumab (Yervoy) is a CTLA-4 checkpoint inhibitor and is used specifically to treat skin melanoma. Some common side effects of checkpoint inhibitors include diarrhea, pneumonitis (inflammation in the lungs), rashes and itchiness, problems with some hormone levels, and kidney infections. Again, more on the mechanics of checkpoint inhibitors in Chapter 6, Cancers.

The reason for the large variety of immunotherapeutic drugs is due to the extensive diversity of proinflammatory mediators in the chronic inflammatory and autoimmune process. To wit, research in immunotherapeutic drugs reaches back into the chemistry of the innate immune system as well. Researchers have found a new way to treat the inflammation involved in chronic diseases such as psoriasis, asthma, and HIV. A group of transmitter substances (cytokines) in the immune system, the so-called IL-1 family in the innate immune system (see Chapters 1 and 2), has been shown to play an important role in many of these diseases by regulating APCs and the body's immune responses [37].

While the biologics include a large number of drug options, all are attempting to regulate (increase or decrease) the immune response. Each has a distinct biochemical effect on different mediators. This gives treating physicians the ability to get a maximal drug effect (and sometimes a definitive diagnosis) by “experimenting” with response(s) to a variety of biologics. Based on elevated or reduced blood levels of cytokines, specific proteins, WBCs, etc., one biologic may produce a better (or lesser) effect than another and sometimes, even reveal the nature of an otherwise undetermined condition. This also confuses the hell out of the public (especially those using a biologic) when they watch a TV commercial promoting a biologic drug for a specific autoimmune condition (e.g., RA) on one station. Then they change channels and see the same drug being promoted for an entirely different condition (e.g., Crohn's Disease). The drugs are specific for individual mediators that occur in multiple autoimmune diseases, and thus, they are nonspecific for any one disease. Make sense?

8. Therapeutic (cellular and genetic) procedures

To state, once again (you can probably tell how important I consider this point to be by now), an autoimmune disease may be organ specific in its clinical presentation (e.g., Crohn's disease, Graves' disease, etc.), or its clinical effects may be diffuse or disseminated in multiple organ systems throughout the body (e.g., SLE, giant-cell arteritis, RA). Thus, treatments

for autoimmune diseases beyond the drug classes we have been discussing, must be targeted for organ-specific therapies, or in diffuse disease, delivered as disseminated treatment throughout the body via cellular and genetic pathways. This is also the case in cancer therapies. Thus, multiple treatment options and approaches are common to both autoimmune diseases and cancers. Among the treatment options common to autoimmune diseases and cancers, besides the drug categories and specific medications (in Table 5.4) we have been discussing, are cell transplantation therapies and genetic procedures.

Stem cell transplantation and immunogenomic (CRISPR-Cas9 and CAR-T cell) therapies have been well received as immunologic and immunogenic therapies. They are rapidly approaching the standard of care for targeted, organ-specific treatments as well as disseminated and genomic therapies. Effectively, stem cell transplantation, CAR-T or CAAR-T cell replacement therapy, and CRISPR-Cas9 (gene editing) have similar applications, though with different therapeutic goals in autoimmune diseases, genetic disorders, cancers and numerous other congenital, acquired and chronic conditions [38]. It is important to note here that these innovative and "disruptive" biomedical and cellular therapies for autoimmune diseases enjoy the benefits that piggyback on the successes of genetic and cancer treatments and vis a versa [39].

I'm probably going to give you more on these procedures than you will feel you might need, and you may be correct, at least presently (as you read this section). But, to use that popular saying I used long ago in the Preface of this book (regarding my love for immunology and genetics), "in the spirit of total transparency" I must tell you that I'm very high on stem cell therapy (regenerative medicine) and therapeutic (cellular and genetic) procedures. I definitely think they will have a growing and significant role in immunology and health care in general going forward. My guess is you will continue to hear more and more about them and very possibly will take advantage of one or more of them regarding your own needs sometime in the future. Thus, I felt it is worth introducing them to you and then letting you be the judge after you read the section as to how much info you feel you need on stem cells, CAR-T and CAAR-T-cell replacement therapy, and CRISPR-Cas9 (gene editing). If I'm right, you'll be happy you read it … I hope.

8.1. Regenerative medicine (stem cell therapy)

Stem cells are cells within the body originating during embryologic development (from totipotent to pluripotent embryonic stem [ES] cells). During early life and growth, these undifferentiated ES cells have the potential to develop into many (and any) different types of adult (somatic) stem cells found in organs and tissues in the body. They also differentiate into red blood cells (erythrocytes), platelets, and white blood cells (leukocytes or WBCs) including neutrophils, basophils, eosinophils, macrophages, monocytes. Of particular interest in this discussion are the

WBCs associated with the immune system which differentiate to including lymphocytes (T-cells, B-cells, natural killer cells) and plasma cells (Fig. 5.2). The adult stem cells serve as a repair system for the body. In some organs, such as the gut and bone marrow, they regularly divide to repair and replace worn out or damaged tissues. In other organs, however, such as the pancreas and the heart, stem cells only divide under special conditions.

Given their unique regenerative abilities, the adult stem cells offer new potentials for treating conditions such as immune disorders, cancers, diabetes, and heart disease. When these cells are used in cell-based therapies to treat disease, it is referred to as regenerative or reparative medicine. The more versatile human embryonic (pluripotent or PSC) stem cells can be harvested through embryos and used for reproductive purposes through in vitro fertilization. This method has met with some religious, ethical, and political resistance. However, in 2006 researchers led by Shinya Yamanaka made a (2012 Nobel Prize winning [40]) breakthrough by identifying conditions that would allow specialized adult cells to be "reprogrammed" genetically to assume a stem cell-like state. This new type of stem cell is called an induced pluripotent stem cell (iPSC) and functions similarly to a natural pluripotent stem cell with the ability to become virtually any cell type of the body. This discovery is *a very big* advance in immunotherapy and beyond since it removes the need for embryonic stem cells with their associated ethical and religious resistance.

The clinical value of stem cells lies in the differentiation of embryonic (pluripotent) stem cells into differentiated adult stem cells. Whereas this process is essential in repair and regeneration of normal healthy tissue in the body, it also plays a more sinister role in cells differentiating into disease-oriented progenitors. Cancers, diabetes, congenital disabilities, and so many other diseases and human disorders are generated through genetic and molecular processes producing differentiation of embryonic and adult stem cells from normal to abnormal. All medical treatments have benefits and risks, but unproven stem cell therapies can be particularly unsafe. The FDA will continue to help with the development and licensing of new stem cell therapies where the scientific evidence supports the product's safety and effectiveness [41].

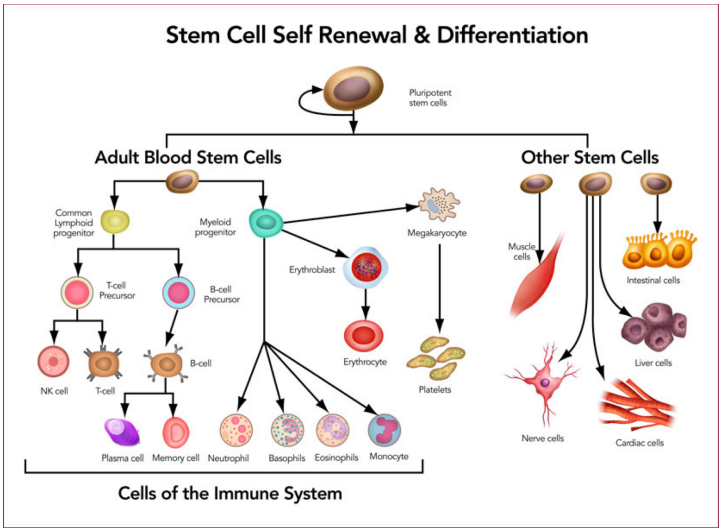


Figure 5.2 Stem cell renewal and differentiation.Stem cells can be readily harvested from bodily tissues and converted into undifferentiated induced pluripotent cells (iPSC—reprogrammed embryonic-like cells capable of developing into any type of human cell) and subsequently into adult blood cells, immune cells, and tissue cells suitable for transplantation into diseased and degenerated organs and body structures. Source: Maharaj Institute of Immune Regenerative Medicine.

While understanding their role in the production of abnormal conditions, stem cells have a number of positive values in testing the effectiveness and safety of new medications, including antitumor therapies and antiinfectives and in the analysis of a broad range of drugs on different cell types. Scientists must be able to precisely control the differentiation of stem cells into the specific cell type on which drugs can be tested. But, perhaps the most important potential application of human stem cells is the generation of cells and tissues that could be used for cell-based therapies ("stem-cell transplantation"). Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including macular degeneration, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and RA.

Stem cells can be readily harvested from bone marrow (called bone marrow transplant) and adipose tissue (a bountiful source of stem cells) and other bodily tissues for conversion into undifferentiated induced pluripotent cells (iPSCs) suitable for transplantation into diseased and degenerated organs and body structures (e.g., diabetes, osteoarthritis, etc.). These iPSC cells then regenerate and begin to replace the abnormal cells with new, normal cells and even potentially as functioning organs (organ morphogenesis [42]) (Fig. 5.2). Currently, muscle and bone tissue are particularly amenable to cell and tissue regeneration.

Stem cell transplantation procedures (also, see the discussion on bone

marrow transplant in “Transplant therapies,” page 140) include a number of methods to delivery targeted therapeutic genes through direct delivery and/or cell delivery (Fig. 5.3). Direct delivery packages the gene into a vehicle such as a genetically engineered retrovirus that is injected into the patient, whereupon it penetrates the genome and thus, is delivered to the targeted organ system. The weakness to this method of delivery includes the random integration of the gene into the patient's chromosomes with unknown, potential adverse effects. Conversely, the cell delivery method removes cells from the patient (embryonic stem cells [ES], HLA or somatic cell nuclear transfer [SCNT]) and introduces the “packaged gene” in the cells (in vitro, i.e., in a test tube) and returns them back into the patient. The use of undifferentiated ES cells as the vehicle for gene retransplant to the patient (autologous transplantation) offers additional specificity to the process where the ES cells can replicate only in the target organ [43].

The objective of stem cell transplantation therapy in immunology is to destroy the mature, long-lived, and auto-reactive immune cells and generate a new, properly functioning immune system. This process has enormous potential in autoimmune diseases, cancers, and other hereditary and acquired genetic mutations resulting in immune system compromise. The patient's stem cells are used in a procedure known as autologous (from “one's self”) hematopoietic stem cell transplantation. First, patients receive injections of a growth factor, that coaxes large numbers of hematopoietic stem cells to be released from the bone marrow into the bloodstream. These cells are harvested from the blood, purified away from mature immune cells, and stored. After sufficient quantities of these cells are obtained, the patient undergoes a regimen of cytotoxic (cell-killing) drug and/or radiation therapy, that eliminates the mature immune cells. Then, the hematopoietic stem cells are returned to the patient via a blood transfusion into the circulation where they migrate to the bone marrow and begin to differentiate becoming mature immune cells [44]. The body's immune system is then restored [45].

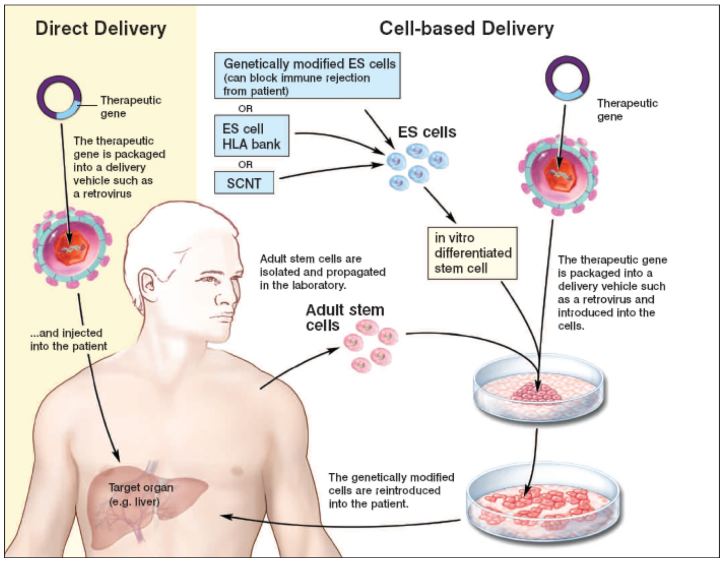


Figure 5.3 Direct and cell-based stem cell therapy.Delivery of a targeted therapeutic gene include direct delivery where the gene is packaged into a vehicle such as a genetically-engineered retrovirus and injected into the patient, whereupon it penetrates the genome. The indirect cell delivery method removes cells from the patient and introduces the "packaged gene" in the cells (in vitro) and returns them back into the patient. Undifferentiated embryonic stem (ES) cells can serve as the vehicle for gene retransplant (autologous transplantation). Source: National Institute of Health, U.S. Dept. of Health and Human Services.

8.2. Immunogenetic and immunogenomic procedures (molecular biology)

The potential for cures is now ready for discussion. (Please take note that I have used the word "cures" very sparingly throughout this book, the only other definitive time being the earlier chapters where I describing the value of "removing the cause" in immune-inflammatory disease.) The only place I consider our (medical care's) potential to achieve a "cure" in health care, especially for autoimmune diseases and cancers (in Chapter 6) lies in the current and evolving genetic therapies we will now discuss. They include CAR-T and CAAR-T cell (replacement therapy), and CRISPR-Cas9 (gene editing). Sometimes referred to as "genetic engineering" or "genetic modification," it can be defined as the direct manipulation of the genome using molecular engineering techniques. Recently developed methods for modifying genes are often called "gene editing." [46] It can be applied in two very different ways: somatic genetic modification and germline genetic modification.

Somatic genetic modification adds, cuts, or changes the genes in some of

the cells of an existing person, typically to alleviate a medical condition. A number of these gene therapy techniques are now FDA approved for specific conditions. Germline genetic modification (quite a difference from "gene editing") is used to "change" the genes in eggs, sperm, or early embryos [47]. A number of these therapies are also FDA approved, but (as of this writing) under intense scrutiny because of serious issues that genetic engineering may go well beyond the science and safety of the field. Bioethical questions also abound regarding potential uses and misuses of this germline bioscience as well as AI applications expanding its potential beyond therapeutic purposes. To wit, some controversial uses of genetic engineering include (but are not limited to):

- Human genetic enhancement: The intentional modification of the human genome to "improve" individuals;
- Human germline genome editing: introducing heritable changes to sperm, eggs, or embryos;
- Eugenics: (Eugenics is from a Greek word meaning "normal genes.") [48] Its modern definition describes it as the attempt to direct human heredity and evolution to ensure procreative advantage to more "desirable" human beings and to discourage or limit reproduction by the less desirables (that sounds like a pretty ugly proposition to me);
- Genetic cloning: Cloning describes the processes used to create an exact genetic replica of another cell, tissue, or organism [49]. The copied material, that has the same genetic makeup as the original, is referred to as a clone. Of course, the use of genetic cloning for monoclonal antibodies is an enormously valuable procedure.

The ethics and pros and cons of all of these techniques are under excruciating analysis and review by international groups. Undoubtedly laws and regulations will be instituted in the coming years to mitigate the dangers of these technologies while maximizing their value in healthcare. As such, let's look at the procedures and their therapeutic applications and implications.

8.2.1. CAR-T and CAAR-T cell therapy (gene replacement)

Chimeric antigen receptor T cells (CAR-T cells) are T cells that have been genetically engineered to give them the new ability to target a specific protein. The receptors are "chimeric" meaning they combine both antigen-binding and T-cell activating functions into a single receptor. The initial premise of CAR-T immunotherapy is to modify T cells to recognize cancer cells to more effectively target and destroy them [50] (more on this to be discussed in Chapter 6). Similar to the cancer treatment by targeting tumor-associated antigens expressed on the surface of tumor cells, CAR-T cells are now being modified to treat autoimmune diseases by targeting

specific autoantigens or antibodies. This type of CAR-T cell immunotherapy is referred to as chimeric autoantibody receptor T (CAAR-T) cell and CAR-Treg (targeting Treg cells [see Chapter 2, page 26] to help regulate and suppress immune activity) based on the suspected autoimmune disease.

CAAR-T-cell immunotherapy (Fig. 5.4) begins by removing a patient's T lymphocytes and transducing them with a DNA plasmid vector (a DNA molecule distinct from the cell's DNA) and engineered to include a manipulated or cloned gene sequence or autologous stem cells targeted for an autoantigen. These modifying T cells are then transferred back into the patient's bloodstream through a single infusion (Fig. 5.4). The modified lymphocytes begin to enhance the patient's immune response by targeting the autoantigen protein. Known as autologous CAAR-T-cell therapy, this treatment is showing promising results in numerous autoimmune diseases [51]. A similar process will be presented in Chapter 6, page 165 and Fig. 6.3 using encoded tumor antigens to elicit a targeted immune response to a cancer.

8.2.2. CRISPR-Cas9 (gene editing)

One of the effective ways of treating autoimmune disease is to identify the "signature" of offending genes (their "gene expression" or the number of RNA molecules they are producing), that is abnormal in autoimmune (and cancer) genes. This identification is accomplished using a technique called "single-cell RNA sequencing" (scRNA-seq), or more specifically, TIDE (for Tumor Immune Dysfunction and Exclusion) for autoimmune genes [52]. With this information, a procedure called CRISPR-Cas9 ("Clustered regularly interspaced short palindromic repeats"—a family of DNA sequences found in the genomes of prokaryotic organisms, i.e., organisms where the DNA is in the cell cytoplasm rather than its nucleus—*this is explained in a bit more understandable language ahead, so feel free to forget this last sentence*) and Cas9, an enzyme sometimes referred to as "the scissor protein." In essence, the procedure is an RNA-guided genome editing technology being used to reengineer T cells.

Immunogenetic Immunotherapy

Chimeric Autoantigen Receptor T cells (CAAR-T)

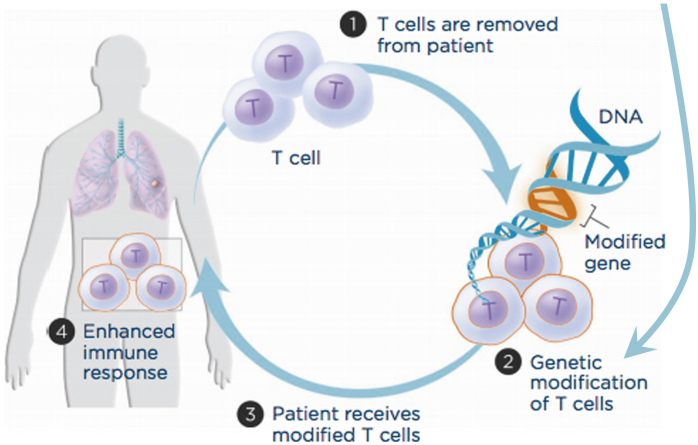


Figure 5.4 Chimeric autoantigen receptor T-cells (*CAART-T*).Immunogenic immunotherapy CAAR-T-cell therapy begins by removing a patient's lymphocytes and transducing them with a DNA plasmid vector (a DNA molecule distinct from the cell's DNA used as a tool to clone, transfer, and manipulate genes) that encodes specific tumor antigens. These modified and targeted lymphocytes are then reintroduced to the patient's body through a single infusion to attack tumor cells. Source: National Institute of Health, U.S. Dept. of Health and Human Services.

Similar to the way bacterial defenses against viral invasion occurs, CRISPR-Cas9 is used to induce genome edits by creating targeted DNA breaks that will trigger specific DNA repair. When considering "next-generation" genetic processing ("central dogma of molecular biology"—see Chapter 3, page 51), it can also control the transcriptional output of genes or alter genome sequences using a process of nucleotide base editing [53]. As these technologies continue to mature, it is becoming increasingly possible to efficiently and accurately alter cellular genomes.

The CRISPR-Cas9 system (Fig. 5.5) creates a small piece of RNA (Cas9) with a short "guide" sequence that attaches (binds) to a specific target sequence of DNA identified by NGS (next generation sequencing—see Chapter 3, page 55) in a genome. The RNA also binds to the Cas9 enzyme and is used to recognize the DNA sequence. The Cas9 enzyme, acting as a "scissor," cuts the DNA at the targeted location. Once the DNA is cut, the cell's DNA uses its repair machinery to add or delete pieces of genetic material, or to make changes to the DNA by replacing an existing segment with a customized DNA sequence [54]. It was first thought that the stitching back together of the genetic material after the CRISPR-Cas9 procedure was random [55]. But subsequent studies using a trained machine learning (ML) algorithm called inDelphi to predict repairs made to DNA snipped with Cas9 confirmed that the edits aren't random at all

[56,57].

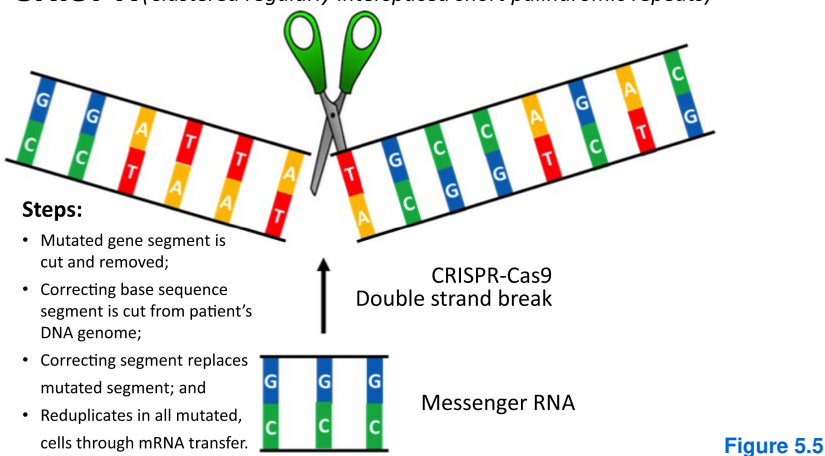


Figure 5.5
CRISPR-Cas9 procedure.CRISPR guide RNAs target specific spots in the genome for the Cas9 enzyme ("genetic scissors") to cut, forming a double-strand break. A machine learning algorithm predicts which types of repairs will be made at a site targeted by a specific guide RNA. Possibilities include an insertion of a single base pair, a small deletion, or a larger change known as a microhomology deletion. Source: National Institute of Health, U.S. Dept. of Health and Human Services.

It is worth noting here that in October 2020, the Nobel Prize in Chemistry was awarded to two molecular biologists, Emmanuelle Charpentier of the Max Planck Unit for the Science of Pathogens Institute for Infection Biology and Jennifer Doudna of the University of California, Berkeley, for the development of this revolutionary genome editing technique often referred to as "genetic scissors."

The unfortunate aspect of these immunotherapeutic procedures (and CAR-T cell therapies) are their exorbitant costs. Notwithstanding the significant benefits these therapies provide, the costs of FDA approved CAR-T cell therapy and the CRISPR-Cas9 procedure range from $373,000 to $875,000 for a single treatment [58]. Also, depending on the type of stem cell procedure, prices can range from $5000 to $25,000 per procedure [59]. Gene therapies are subject not only to the regulatory structure of the FDA, but also to the Office of Biotechnology Activities, and the Recombinant DNA Advisory Committee. Excessive regulatory oversight creates an elongated and expensive route to approval. By one estimate, approval for a gene therapy costs nearly $5 billion (five times as much as the average cost of FDA drug approvals [60]). Some insurers are beginning to provide partial coverage of FDA approved gene therapies, but experimental treatments receive no third-party coverage other than limited humanitarian exemptions. Hopefully, as with other major therapeutic discoveries, the costs in providing the technology will reduce over time.

8.2.3. CRISPR-Cas13 and mRNA screening

A new CRISPR-Cas13 RNA screen has been developed to establish guide RNAs for the COVID-19 coronavirus and human RNA segments that could be used in vaccines, therapeutics and diagnostics. Let's defer a full discussion on this technology to Chapter 7 on infectious diseases, pandemics, and of course, COVID-19.

8.3. Transplant therapies

One other branch of immunotherapies of profound importance is that of organ, tissue, and cell transplantation. So too are the profound immunological challenges presented in such therapies. All of the considerations of innate and adaptive immunity come into play with homograph (*aka* allograph) transplantation, that is transplantation from one donor to another of the same species (humans for this discussion) but different genetic (genotype) makeup. Between the basic immunologic tenet of "self versus nonself" to the anamnestic (memory) response of the immune system, success with homographic transplantation needs intricate blood typing, cellular (receptor), and genetic matching of donor and recipient.

Organ failure (heart, liver, kidneys, etc.) is not unusual in humans, no less tissue injury and destruction by dermatological diseases (autoimmune and otherwise, e.g., accidents, and particularly, burns). So, the need to reduce (suppress) the immune system's natural reaction to a "foreign transplant" was an obvious necessity in homographic transplantation. Immunosuppressive drugs, from steroids to the strongest immunotherapeutic agents, proved capable of doing the job of controlling the immune response. The introduction of the immunosuppressant drug, cyclosporine in 1983 revolutionized transplant medicine. But needless to say, these drugs would also reduce the patient's fundamental (T cell, B cell, etc.) defenses against other nonself-invader, particularly opportunistic infectious agents.

Another recognition of homographic transplantation developed with the Nobel Prize winning discovery of isoantigens (or alloantigen or human leukocytic antigen, HLA), genetically determined antigens in humans (all slightly different—like fingerprints) derived from the "selfrecognition" major histocompatibility complex, MHC (see Chapter 1, page 11). Isoantigens (blood antigens or HLA complex) are present in some members of the human species (subset) and not others. Transfusion (blood) or transplantation of isoantigens into a donor without isoantigens will produce an immune antibody response (alloimmnuity with alloantibodies) and result in a blood transfusion reaction or graft rejection (Type II cytotoxic hypersensitivity reaction, from Chapter 2, page 30). So, it is critical that donor blood types and isoantigens are properly matched with recipients.

The discovery of isoantigens led to a more dynamic form of

transplantation, namely bone marrow transplant. Given that the bone marrow is a principal site of stem cell, blood cell, and immune cell development, its value in providing a “new” immune system to a qualified recipient (i.e., isoantigen match) becomes obvious in treating autoimmune diseases and cancers. Bone marrow transplants may use cells from your own body (autologous transplant) or from a donor (allogeneic transplant). In either case, with a proper donor, the stem cells will yield a new, hopefully revitalized and disease-free immune system. Through combining these newly developed immunotherapeutic procedures, new treatment modalities including xenotransplantation may be viable alternate to allogenic transplantation. Recently (Januray 7, 2022), a pig heart genetically modified by CRISPR-Cas9 was successfully implanted in a 57 year-old male. As of this reporting date (February 7, 2022), the patient is doing well [60a].

9. Brief research summaries on autoimmune diseases

(Reference citations for each research study presented below can be found in the corresponding footnote. Also, a listing of available scientific reference sources and databases used by the author are included in the book's Acknowledgments.)

1. Researchers used the ImmunoChip dataset containing 18,227 Crohn's disease patients and 34,050 healthy controls enrolled and genotyped by the International IBD Genetics Consortium to be reanalyze via a set of ML methods. They managed to detected nearly all the genetic variants previously identified by human genome-wide association studies among the best predictors, plus additional predictors with lower effects. Overall, such an approach may provide a more superior alternative method to traditional experimental colitis method of understanding the disease by allowing analysis of complex systems through crunching of big data [61].
2. Artificial intelligence (AI) applications are being studied in MS, RA and IBD, generating models using two data types, random forests and support vector machines. These are commonly used AI data applications for many diseases. Clinical studies in models using genetic data were created for the majority of autoimmune diseases. The applications are categorized into six broad topics: patient identification, risk prediction, diagnosis, disease subtype classification, disease progression and outcome, and monitoring and management. Results are yielding new and valuable information in the diagnosis and management of autoimmune diseases [62].
3. A study was conducted to determine if animal, dietary,

recreational, or occupational exposures are associated with MS risk. The least absolute shrinkage and selection operator regression methods were used to identify a subset of exposures with potential relevance to disease in a large population-based, case–control study. There was a suggestive association of pesticide exposure with having MS among men, but only in those who were positive for HLA-DRB1. Future investigative methods may be useful for of concomitant MS risk or prognostic factors [63].

4. CRISPR-Cas9 tools have accelerated the pace of genomic research by permitting highly efficient knockouts or edits of virtually any gene in cells or model organisms. Multiple CRISPR-Cas9–based clinical trials are in progress or are expected to begin soon. Although Cas9-engineered cells haven't yet demonstrated efficacy at scale, early trial results suggest that such cells are stable and don't cause acute adverse reactions in humans. Long-term safety is yet to be determined. Current applications largely focus on single-gene disorders for which gene editing can be carried out ex vivo on appropriate cells, such as bone marrow hematopoietic stem cells in the case of sickle cell anemia. Exploration is under way to develop delivery systems that can target the gene-editing apparatus to the appropriate tissue in vivo [64].
5. ML approaches were employed to integrate gene expression data from three SLE data sets and used them to classify patients as having active or inactive disease as characterized by standard clinical composite outcome measures. Both raw whole blood gene expression data and informative gene modules were employed with various classification algorithms. The use of gene modules rather than raw gene expression was more robust, achieving classification accuracies of approximately 70% regardless of how the training and testing sets were formed [65].
6. MS: An AI algorithm was created to predict the expanded disability status scale (EDSS) score of patients with MS at 2years solely based on age, sex and fluid attenuated inversion recovery (FLAIR) MRI data. The algorithm combined several complementary predictors: a pure deep learning predictor based on a convolutional neural network that learns from the images, as well as classical machine-learning predictors. The method predicted two-year clinical disability in patients with MS with a mean EDSS score error of 1.7. This supports the use of such a model to predict EDSS score progression [66].
7. Type 1 diabetes: An algorithm that provides weekly insulin dosage recommendations to adults employs a unique virtual platform to generate over 50,000 glucose observations to identify causes of hyperglycemia or hypoglycemia and

determine necessary insulin adjustments from a set of 12 potential recommendations. The algorithm achieves an overall agreement with board-certified endocrinologists of 67.9%. These data indicate that the algorithm allows for early identification of dangerous insulin regimens and may be used to improve glycemic outcomes and prevent life-threatening complications in people with T1D [67].

8. Guillain-Barre syndrome (GBS): GBS includes acute motor axonal neuropathy, acute motor and sensory axonal neuropathy, and pharyngeal-cervical-brachial weakness. Newly developed technologies, including metabolite analysis, peripheral nerve ultrasound, and feature selection, are facilitating more accurate diagnosis of axonal GBS. Nevertheless, some key issues, such as genetic susceptibilities, remain unanswered, and moreover, current therapies bear limitations [68].
9. In an effort to apply AI to the challenging task of classifying thyroid nodules in Graves' disease, an image similarity algorithm showed accuracy that is similar, and in some aspects better, than the best available ultrasound-based classification systems. By using image similarity AI models, subjectivity is eliminated resulting in a decrease in the number of unnecessary biopsies by as much as 50%. A deep learning model was also used to process all available images for 482 nodules from patients who underwent a biopsy or thyroid surgery. Overall, 66 nodules were malignant in the training set and 33 were malignant in the test nodules. Overall, the system's accuracy was 81.5%. The results suggest that the use of the image similarity AI system could result in a 57.3% reduction in biopsies [69].
10. In 1year in the United States, it was reported that 31% of medical lawsuits were related to either an inordinate delay in the diagnosis or failure to make the correct diagnosis. It is anticipated that precision medicine coupled with AI will help healthcare providers stay abreast of current literature and predict individual susceptibility to primary or secondary autoinflammatory and autoimmune conditions [70].
11. Identification of patients with autoimmune diseases was studied utilizing ML methods and employing natural language processing methods from electronic medical records. The algorithms were intended to replace International Classification of Diseases billing codes that have error rates of between 17.1% and 76.9% due to inconsistent terminology. The AI process improved the efficiency of algorithms for this purpose. Prediction of disease risk and identification of novel risk factors through feature selection was documented for IBD, type 1 diabetes (T1D), RA, SLE, and MS. ML specifically for early diagnosis was specified by seven studies for the later onset degenerative conditions MS and RA. Disease progression and

outcome was a focus for 27 studies. Other considered issues were disease severity, treatment response, and survival prediction. Disease progression and outcome was the second-most prevalent area for model development. The majority of the data used was clinical, with very few papers utilizing “omic” data. These models could be applied to more difficult tasks that reflect the complexity of autoimmune disease. The advances have the potential to bring personalized medicine closer for patients with complex and chronic disease [71].

12. Autoimmune diseases are mostly characterized by autoantibodies in the patients' serum or cerebrospinal fluid, representing diagnostic or prognostic biomarkers. Research has focused on single autoantigens or panels of single autoantigens. Researchers are now broadening their focus by addressing the entire autoantigen repertoire in a systemic “omics-like” (analyzing large amounts of data) approach. This aims to capture the enormous biodiversity in the sets of targeted antigens and pave the way toward a more holistic understanding of the character of antibody-related humoral immune responses. Clusters of autoantigens can be identified that share certain functional or spatial properties, or clusters of patients comprising clinical subgroups potentially useful for patient stratification. This may enhance the understanding of autoimmune diseases in a more comprehensive way compared to current single or panel autoantibody approaches [72].
13. Unraveling the genetic and environmental underpinnings of autoimmune disease has become a major focus at the National Institute of Environmental Health Sciences of the National Institute of Health. The process of identifying adverse genetic sites (likely multiple mutations) in the person's genome is overwhelming. As we described in Chapter 3, the potential for those mutations in the sequencing of the four base compounds within the 20,000 to 25,000 genes in the human genome exceeds 2.5×10^{20} possibilities spread among the 37.2 trillion somatic cells. Thanks to big data analytics and deep learning (AI methods), genetic loci for immune diseases (immunodeficiencies) are now being identified in a timely diagnostic manner (days to weeks vs. months to years). This research is helping to better identify genetic mutations and their associated disease states combined with the new FDA approved cellular and gene therapies (presented above). It is creating new horizons in the treatment, management, cures and prevention of autoimmune diseases [73].

14. Advances in “omics” technologies (e.g., epigenomics, genomics, transcriptomics, proteomics, metabolomics, etc.), also called, systems-based approaches, are now utilized to identify

molecular targets including biomarkers that can reveal the disease state or the ability to respond to a specific treatment. This capability is providing scientists and clinicians with the ability to generate datasets consisting of molecular insights of autoimmune disease pathogenesis [74].

15. AI algorithms now allow categorization of patients based on their specific differences through screening a patient's genome, transcriptome, proteome, epigenome, immunome, and microbiome. Integrating the omics datasets using systems biology-based approaches may advance understanding of the underlying causative factors in individual patients. This ability could contribute to the diagnosis and prognosis of autoimmune diseases, and whether such diagnostic information could assist with predictions of therapy efficacy and adverse effects. This offers enormous potential for personalized medicine (see Chapter 3, page 57) in autoimmune diseases and evaluating the use of big data in disease management [75].

Chapter highlights (key points and paradoxical-related information)

1. Among the multiple paradoxes associated with autoimmune diseases, the threshold question is “why does the body interpret ‘self’ as ‘foreign’ (nonself) and treats it as an antigen, specifically an ‘autoantigen’?”
2. Another paradox of autoimmune diseases are their higher prevalence in females with some theories including male testosterone protection, pregnancy factors, greater body fat in females, lifespan, and even the “hygiene hypothesis” compromising the microbiome and sexual dimorphism.
3. Perhaps the most credible and validated, science-based theory regarding female bias in autoimmune diseases lies in the immunogenomic science of X chromosome inactivation (XCI) or “lyonization” and its intimate relationship with microRNA.
4. Beyond a prolonged inflammatory process producing autoimmune disease, other theories of the suggested pathogenesis of autoimmune diseases include the patient’s genome; environmental factors; accumulation of proinflammatory cytokines; rogue B cells; epitope spreading; and the microbiome.
5. In that chronic inflammation and its perivascular characteristics (see Chapter 4) are the pathological basis of autoimmune disease, its clinical presentation(s) can be organ specific or multisystem involvement.

6. There are over 88 clinical conditions classified as autoimmune diseases effecting greater than 8% of the general population, with the top 10 being conditions highly recognizable, some like rheumatoid arthritis, systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), and multiple sclerosis.
7. Again, because of the chronic inflammatory etiology of autoimmune diseases, afflicted patients are categorized as chronic disease patients, and oftentimes are comorbidity patients.
8. Treatment for autoimmune diseases, as with chronic inflammation (in Chapter 4) is categorized as "nonspecific" immunotherapies which include biologics like DMARDs (disease-modifying antirheumatic drugs); hydroxychloroquine (you've heard of that one, I'm sure!); methotrexate; sulfasalazine; checkpoint inhibitors; more in Chapter 6; and of course, monoclonal antibodies.
9. Emerging as a strong adjunct to pharmacologic immunotherapies are cellular and genetic (molecular biology) therapeutic procedures sometimes referred to as "genetic engineering" or "genetic modification" including CAR-T and CAAR-T cell (replacement therapy), CRISPR-Cas9 (gene editing), and stem cell therapy (regenerative medicine).
10. Beyond immunopharmacothearpies and molecular biologic procedures, tissue and organ transplantation therapy continue to advance in organ-specific autoimmune disease with the use of adjunctive immunosuppression drugs.

References

1. Fairweather D, Rose N.R. Women and autoimmune diseases. *Emerg Infect Dis* . November 2004;10(11):2005–2011.
2. Jacobson D.L, Gange S.J, Rose N.R, Graham N.M. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol* . September 1997;84(B):223–243.
3. Larson C. *New theories explaining why women are more susceptible to autoimmune disease than men* . Managed Healthcare; June 10, 2020.
4. Mousavi M.J, Mahmoudi M, Ghotloo S. Escape from X chromosome inactivation and female bias of autoimmune diseases. *Mol Med* . 2020;26:127.
5. Youness A, Miquel C.H, Guéry J.C. Escape from X chromosome inactivation and the female predominance in autoimmune diseases. *Int J Mol Sci* . 2021;22(B):1114.
6. Macfarlane L.A, Murphy P.R. MicroRNA: biogenesis, function

and role in cancer. *Curr Genom* . January 23, 2021;11(7):537–561.
7. Orbai A.M. *Autoimmune disease: why is my immune system attacking itself* . Johns Hopkins Health; 2019.
8. Kuchroo V.K, Ohashi P.S, Sartor R.B, et al. Dysregulation of immune homeostasis in autoimmune diseases. *Nat Med* . 2021;18:42–47.
9. Tsokos G.C. Autoimmunity and organ damage in systemic lupus erythematosus. *Nat Immunol* . 2020;21:605–614.
10. Satoab S, Takaokaab A. Subchapter 39A – interleukins. In: 2nd ed. *Handbook of hormones* . vol. 1. Academic Press; 2021:437–439. .
11. Disease Development. How do autoimmune diseases unfold? *Johns Hopkins Med Pathol* . 2019.
12. Kelly P.N. Cells gone rogue. *Science* . March 13, 2020;367(6483):1208.
13. Medline. *Autoimmune disorders* . U.S. National library of medicine. U.S. Department of health and human Services. National Institutes of Health; July 2, 2020.
14. Moudgil K.D. Viewing autoimmune pathogenesis from the perspective of antigen processing and determinant hierarchy. *Immunology* . 2020:329–339.
15. Wang E.Y, Mao T, Klein J, et al. Diverse functional autoantibodies in patients with COVID-19. *Nature* . 2021;595:283–288.
16. Ibid. Moudgil. 14.
17. Søren E, Degn S.E, van der Poel C.E, Firl D.J, et al. Clonal evolution of autoreactive germinal centers. *Cell* . August 24, 2017;170(Issue 5):P913–P926 E19.
18. Jiao Y, Wu L, Huntington N.D, Zhang X. Crosstalk between gut microbiota and innate immunity and its implication in autoimmune diseases. *Front Immunol* . 2020;11:282.
19. Markowiak-Kopeć P, Śliżewska K. The effect of probiotics on the production of short-chain fatty acids by human intestinal microbiome. *Nutrients* . 2020;12(C):1107.
[19a] Gruber C.N, Patel R.S, Trachtman R, et al. Mapping systemic inflammation and antibody responses in multisystem inflammatory syndrome in children (MIS-C). *Cell* . November 12, 2020;183(4):982–995.
20. Autoimmune diseases. Cleveland Clinic; July 21, 2021.
21. Ibid. Autoimmune diseases. 13.
22. *What is precision medicine. MedlinePlus* . NIH. National U.S. Library of Medicine; September 22, 2020. USA.gov.
23. Chen L, Deng H, Cui H, et al. Inflammatory responses and

inflammation-associated diseases in organs. *Oncotarget* . January 23, 2019;9(6):7204–7218.
24. Primary immunodeficiency. Mayo Clinic; January 30, 2020.
25. Eustice C. *Autoimmune disease types and treatment* . VeryWellHealth; May 6, 2019.
26. Finer N, Garnett S.P, Bruun J.M. COVID-19 and obesity. *Clin Obes* . April 27, 2020;10(B):e12365.
27. Sampson S, Watson S. *Autoimmune diseases: types, symptoms, causes, and more* . Healthline; March 26, 2019.
28. Carteron N. *A list of autoimmune diseases and their symptoms* . Medical News Today; June 29, 2020.
29. Ibid. Autoimmune Diseases. 13.
30. Hayterab S.M, Cookac M.C. Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. *Autoimmun Rev* . August 10, 2012;11:754–765.
[30a] Ibid. Gruber et al. 19a.
31. *Type 1 diabetes. Genetics home reference* . U.S. National Library of Medicine; October 15, 2019.
32. Marovich M, Mascola J.R, Cohen M.S. Monoclonal antibodies for prevention and treatment of COVID-19. *JAMA* . 2020;324(A):131–132.
33. Ogbru O. *Biologics (biologic drug class)* . MedicineNet; 2019.
34. Cohen S, Cannella A. *Patient education: disease-modifying antirheumatic drugs (DMARDs) (Beyond the Basics)* . February 28, 2019.
35. Ibid. Ogbru. 33.
36. Hui E. Immune checkpoint inhibitors. *J Cell Biol* . 2019;218(B):740–741.
37. Falkesgaard Højen J, Vindvad Kristensen M.L, McKee A.S, et al. IL-1R3 blockade broadly attenuates the functions of six members of the IL-1 family, revealing their contribution to models of disease. *Nat Immunol* . 2019;20(9).
38. Zhang Z, Zhang Y, Gao F, et al. CRISPR/Cas9 genome-editing system in human stem cells: current status and prospects. *Mol Ther Nucleic Acids* . 2017;9:230–241.
39. Immunotherapies for autoimmune diseases. *Nat Biomed Eng* . April 5, 2019;3:247. .
40. https://www.nobelprize.org/prizes/medicine/2012/press-release/.
41. FDA Warns About Stem Cell Therapies. U.S. Food and Drug Administration; September 3, 2019.
42. Eguizabal C, Aran B, Geens M, et al. Two decades of embryonic stem cells: a historical overview. *Hum Reprod* . 2019:1–17. doi: 10.1093/hropen/hoy024.

43. Zwaka T.P. *Use of genetically modified stem cells in experimental gene therapies* . National Institutes of Health, U.S. Department of Health and Human Services; August 10, 2020.
44. National Cancer Institute, . *Dictionary* . National Institute of Health; 2019.
45. NIH. Stem Cell Information, . *Autoimmune diseases and the promise of stem cell-based* . National Institutes of Health, U.S. Department of Health and Human Services; August 10, 2020.
46. Solomon M.Z. *Gene editing humans: it's not just about safety* . Scientific American; August 10, 2019.
47. Editorial. Germline gene-editing research needs rules. *Nature* . March 13, 2019;567:145.
48. Friedmann T. Genetic therapies, human genetic enhancement, and … eugenics? *Gene Ther* . July 4, 2019;26:351–353.
49. Medline Plus, . *Cloning. U.S. Department of health and human Services* . National Institutes of Health. U.S. National Library of Medicine; April 19, 2019.
50. Minutolo NG, Hollander EE, Powell Jr DJ. The emergence of universal immune receptor T cell therapy for cancer. Front Oncol March 26, 2019. https://doi.org/10.3389/fonc.2019.00176.
51. Shank B.R, Do B, Sevin A, et al. Chimeric antigen receptor T cells in hematologic malignancies. *Pharmacotherapy* . 2017;37(B):334–345.
52. Benhenda M. *How to better predict cancer immunotherapy results* . Medium AI Lab; May 22, 2019.
53. Clark M.M, Hildreth A, Batalov S, et al. Diagnosis of genetic diseases in seriously ill children by rapid whole-genome sequencing and automated phenotyping and interpretation. *Sci Transl Med* . April 24, 2019;11(489).
54. Genetics Home Reference, . *What are genome editing and CRISPR-Cas9? NIH* . USA.gov: National U.S. Library of Medicine; October 1, 2019.
55. van Overbeek M, Capurso D, Carter M.M, et al. DNA repair profiling reveals nonrandom outcomes at Cas9-mediated breaks. *Mol Cell* . August 18, 2016;63(Issue 4):P633–P646.
56. Shen M.W, Sherwood R, et al. Predictable and precise template-free CRISPR editing of pathogenic variants. *Nature* . 2018;563:646–651.
57. Allen F, Parts L, et al. Predicting the mutations generated by repair of Cas9-induced double-strand breaks. *Nat Biotechnol* . 2019;37:64–72.
58. March R.J. *Why this new gene therapy drug costs $2.1 million 2019* . Foundation for Economic Education; June 3, 2019.

59. Hildreth C. *Cost of stem cell therapy and why it's so expensive* . BioInformant; November 21, 2018.
60. Ramina G. *Regulation and oversight of gene therapy in the US* . Regulatory Focus.org; February 2017.
[60a] Reardon S. First pig-to-human heart transplant: what can scientists learn? *Nature* . 2020;601:305–306.
61. Romagnoni A, Jégou S, Van Steen K, et al. Comparative performances of machine learning methods for classifying Crohn disease patients using genome-wide genotyping data. International Inflammatory Bowel Disease Genetics Consortium (IIBDGC). *Sci Rep* . July 17, 2019;9(1):10351. .
62. Stafford I.S, Kellermann M, Mossotto E, et al. A systematic review of the applications of artificial intelligence and machine learning in autoimmune diseases. *NPJ Digit Med* . March 9, 2020;3:30.
63. Mowry E.M, Hedström A.K, Gianfrancesco M.A, et al. Incorporating machine learning approaches to assess putative environmental risk factors for multiple sclerosis. *Mult Scler Relat Disord* . August 24, 2018:135–141.
64. Broeders M, Herrero-Hernandez P, Ernst M.P.T, et al. Sharpening the molecular scissors: advances in gene-editing technology. *iScience* . 2020;23 100789-100789.
65. Kegerreis B, Catalina M.D, Bachali P, et al. Machine learning approaches to predict lupus disease activity from gene expression data. *Sci Rep* . 2019;9:9617.
66. Roca P, Attye A, Colas L, et al. Artificial intelligence to predict clinical disability in patients with multiple sclerosis using FLAIR MRI. *Diagnost & Interv Imag* . July 7, 2020;101(12):795–802.
67. Tyler N.S, Mosquera-Lopez C.M, Wilson L.M, et al. An artificial intelligence decision support system for the management of type 1 diabetes. *Nat Metab* . 2020;2:612–619.
68. Shang P, Zhu M, Wang Y, et al. Axonal variants of Guillain-Barré syndrome: an update. J Neurol March 5, 2020;268(7):2402–19.
69. Melville N.A. *AI thyroid nodule classification could reduce biopsies by 50%* . Medscape Medical News > Conference News; November 7, 2019.
70. Pinal-Fernandez I, Mammen A.L. On using machine learning algorithms to define clinically meaningful patient subgroups. *Ann Rheum Dis* . June 21, 2019 doi: 10.1136/annrheumdis-2019-215852.
71. Stafford I.S, Kellermann M, Mossotto E, Beattie R.M, MacArthur B.D, Enn

review of the applications of artificial intelligence and machine learning in autoimmune diseases. *NPJ Digit Med* . March 9, 2020;3:30.
72. Moritzae C.P, Paul S, Stoevesan O, et al. Autoantigenomics: holistic characterization of autoantigen repertoires for a better understanding of autoimmune diseases. *Autoimmun Rev* . February 2020;19(2).
73. National Institute of Environmental Health Science. Autoimmune disease. NIH; 2019. USA.gov.
74. Seyhan A.A, Carini C. Are innovation and new technologies in precision medicine paving a new era in patients' centric care? *J Transl Med* . April 5, 2019;17(1):114.
75. Seyed N.S, Madgwick M, Sudhakar P, et al. Big data in IBD: big progress for clinical practice. *BMJ* . February 28, 2020;69(8).

6: Cancer

immunology's cruelest enemy and greatest challenge

Abstract

As the second leading cause of death, cancer is generally considered the most feared disease due to its frequently unrelenting clinical course. On a positive note, there has been a decline in the cancer death rate by 29% from 1991 to 2017. Its etiology is known to be a DNA genetic mutation (oncogenesis) producing abnormal cells that divide uncontrollably and have the ability to infiltrate and destroy normal body tissue. There are numerous theories regarding cancer mutations including oncoevolution (pro-oncogenes promoting cell division); tumor suppressor gene, p53 ("guardian of the genome"); environmental factors (e.g., smoking, pollution, chronic irritation); infectious causes, particularly viruses; X chromosome inactivation and microRNA; epigenetics; the microbiome; and more. The association between cancer and the immune system lies in novel immunomodulating therapies being used separately and in combination with chemotherapies and radiation therapy. Monoclonal antibodies used alone and in combination are showing great promise as are gene editing (CRISPR-Cas9) and gene replacement (CAR-T cell) therapies.

Keywords

Cancering; CAR-T cell; CRISPR-Cas9; Gene editing; Gene replacement; Guardian of the genome; Immuno-oncology; Immunotherapy; Microbiome; MicroRNA; Oncoevolution; p53; Stem cell therapy; X chromosome inactivation (XCI)

> *The immune system's goal is to protect the body against invaders either from without, such as microbes, or from within, such as cancers and different types of neoplastic transformation.*
>
> *Anthony S. Fauci.*

1. Introduction

You have probably seen the signs by now, the popular "MD Anderson Cancer Center" signs with a bold red slash mark through the word

. You've just gotta love it. I doubt there are many words in the human vocabulary that engender more anxiety, uneasiness, and fear than the word “cancer.” It's so near and painful to almost all of us with either an unfortunate direct, personal experience with the disease or agonizing over a loved one, family member or friend suffering through a cancer diagnosis. So, kudos to MD Anderson (or whoever created their signage) for “crossing it out” as is everyone's hope. Thank you.

2. “Cancering”

There was a strong temptation on my part to title this chapter “Cancering.” To understand cancer, one must not think of it as a noun, but rather as a verb. Ironically, while doing my research for this Chapter, I came across an article by a world-renowned cancer expert, W. Daniel Hillis, who used the word “cancering.” [1] He even begins his lengthy, two-part article with the statement, “We make a mistake when we think of cancer as a noun.” I mention Dr. Hillis' comment for three reasons. First, I want to make sure no one reading this book thinks I plagiarized the word “cancering” without due recognition to the originator (if only I had beat him to press!). Second, frankly, I'm so damn proud of myself for independently thinking up a unique premise about cancer, even-though it was thought of previously by a recognized cancer expert (at least it puts me in good company). And finally, I want to urge you to consider reviewing or reading (also available on audio) the excellent article by Dr. Hillis. Part 1 is a scholarly and in-depth study in molecular biology, but Part 2 is clinical with some interesting discussions at a very understandable level.

Now a quick explanation of “cancering.”

As you will recall from the discussion back in Chapter 3 (page 55) on genetics and genomics by the numbers, “…, the rate of acquired mutations in the human genome (with about 37 trillion somatic [body] cells) is in the trillions.” As we stated regarding that phenomenal calculation, “… only an infinitesimal amount of them (less than 60 per gene), override “apoptosis” to produce genetic disorders and disease.” Nonetheless, those mutations are continually occurring, and given the rules of large number combinations and probabilities, virtually all mutations have the potential to become irregular, accumulate, or mutate into a cancer [2]. Thus, if you follow the mathematical law of large numbers, it follows that “If you live long enough (or your luck runs out earlier), you will get cancer.” [3] Thus, throughout our lives, we are all “cancering.”

3. The incidence and prevalence of cancer

There are over 185 types of cancers, according to the National Cancer Institute that also lists the most common cancers (Table 6.1). Leading the list of the top 10 cancers in America [4] (Table 6.2) is skin cancer (I've had

two Mohs procedures for basal cell carcinoma [BCC] which are “no fun”) followed by lung cancer which is the leading cause of cancer deaths and the second leading cause of all deaths in America [5]. Thus, given lung cancer, according to the Center for Disease Control, cancers are the second leading cause of death in America, second only to cardiovascular deaths (see Chapter 4, Table 4.4, page 85). Tragically, in 2020 COVID-19 became the third leading cause of death (345,323) in the U.S. just behind heart disease and cancer [6].

(Update: As part of my proofreading of this manuscript in late 2021, the earlier statistic quoted above has tragically escalated to over 700,000 deaths and now the leading cause of death in the U.S [7], How sad to have ever let that happen.)

Indeed, with cancer, we are dealing with a devastating disease that is being better understood with an expanding commitment to immunologic, genetic, and cancer research. On a positive note, a recent study (January 2020) showed a decline in the cancer death rate by 29% from 1991 to 2017. This included a 2.2% drop from 2016 to 2017, the most significant single-year reduction in cancer mortality ever reported according to the American Cancer Society's annual report on cancer rates and trends. The 26-year decline is driven primarily by a long-term decrease in death rates for the four major cancers; lung, colorectal, breast, and prostate [8]. Recent mortality declines were also dramatic for melanoma of the skin, while long-term rapid increases in liver cancer mortality have decreased in women and stabilized in men. The accelerated drops we are seeing are likely due, at least in part, to the improved diagnosis and management of the common cancer types (Table 6.1 above) as well as more public health education and messaging about cancer prevention (e.g., smoking cessation advertising). Also, according to William G. Cance, M.D., chief medical and scientific officer for the American Cancer Society, immunotherapy has had a profound effect on our ability to treat and control cancers (I guess this might be a nice time to add immunotherapy to “our best friend” list in immunology.)

Table 6.1

- Bladder cancer
- Breast cancer
- Colon and rectal cancer
- Endometrial cancer
- Kidney cancer
- Leukemia
- Liver cancer
- Lung cancer
- Melanoma
- Non-Hodgkins lymphoma
- Pancreatic cancer

- Prostate cancer
- Thyroid cancer

Common cancer types.

Source: National Cancer Institute, 2019.

Table 6.2

1. Skin cancer
2. Lung cancer
3. Prostate cancer
4. Breast cancer
5. Colorectal cancer
6. Kidney (renal) cancer
7. Bladder cancer
8. Non-Hodgkin's lymphoma
9. Thyroid cancer
10. Endometrial cancer

Top 10 (10) cancers in America.

Source: Louis J. Catania © 2022.

Sadly, as a late edition to this otherwise positive news about cancer rates, during manuscript proofing of this book, new data has indicated a resurgence in the rates of cancer development and mortality [9]. Among one million patients studied between 2010 and 2019 in 204 countries, there was greater than a 26% increase in the rate of new cancers. The largest percentage increase in incidence and mortality during that last decade occurred in the lower socioeconomic populations. Contributing and exacerbating this distressing trend are the direct and indirect effects of COVID-19 over the past two years. The virus has been identified as a significant risk factor in multiple ways. The immunocompromised and immunosuppressed cancer patient becomes more vulnerable to SARS-CoV-2 infection and increased mortality risk, especially in a hospital environment common in cancer care [10]. Epidemiologically, the pandemic has decreased access and caused delays in early cancer diagnosis and care due to the increased inaccessibility in hospital and medical care secondary to the over-burdened healthcare system from COVID-19 patients. This dynamic has also resulted in increased cancer mortality rates and avoidable cancer deaths since early 2020 [11].

4. Description and etiologies of cancers

Inherited genetic disorders result in gene alterations in virtually every cell in our body [12]. As a result, these disorders tend to affect many tissues, organs, and body systems. Often, supportive and palliative treatment approaches are available to manage some of the associated signs and symptoms of significant diseases. For example, disorders associated with heart defects might be treated with surgery to repair the defect or with a heart transplant. Inborn errors of metabolism disrupt the production of specific enzymes that dietary changes or replacement therapies may benefit and help prevent immediate and future complications. And when genetic screening identifies an inherent risk in one's genome (e.g., a known cancer gene such as BRCA1, BRCA2, or PALB2 gene for breast cancer), management may include counseling, more frequent cancer screening, or even preventive (prophylactic) surgery to remove the tissues at highest risk of becoming cancerous (e.g., preventive mastectomy).

At the risk of becoming a real nuisance, if not downright annoying, allow me to quickly defend my use of the word “disorder” a few times in the previous paragraph. I am sure you recall my somewhat droning differentiation of the term “disorder” from “disease” back in the book’s Preface and again in Chapter 4, page 88 in defense of my theory of chronic inflammation being the basis of *all* “disease.” I’m sure there are some folks reading the previous paragraph thinking, “the old boy has contradicted his own theory by using ‘disorder’ regarding “heart defects,” “inborn errors of metabolism,” and “gene abnormalities.” Not so. These abnormalities fit the definition of “disorders” as defined in the Preface and Chapter 4 as “…any deviation from or interruption of normal structure or function.” Now please understand, I am not trying to nitpick or be defensive as much as making a relevant point as we enter this discussion on cancer.

We should understand that while the origins of cancers begin as a “… deviation from or interruption of normal structure or function,” i.e., “disorders,” what we know as cancer, really is a disease, “…an abnormal biological process (a pathology) with a specific cause (*disorder*) and identifiable characteristics (signs and symptoms).” And my point is that “cancer,” the disease, is in fact, chronic inflammation.

I rest my case! But after making such a fuss, I better defend it, yet again, by the end of this chapter.

4.1. Random genetic mistakes

In our immunology and genetics discussions up to this point, we have discussed environmental factors (carcinogens) and radiation-caused mutations that may contribute to the development of cancer. The damage to our DNA through both injury and chronic irritation (remember our comments on smoking in Chapter 4?) all can lead to cumulative mutations and resultant “cancering.” But up to now, we haven't considered the possibility of a random mistake (oncogenesis) in one of those trillions of normal DNA replications that escape apoptosis and result in a cancer-

causing mutation [13]. A series of these mutations (carcinogenesis) in a specific gene (oncogene) class can “de novo” transform a normal cell into a neoplastic (cancer) cell [14].

4.2. Epigenetics

Beyond “a random genetic mistake” producing cancer, there are several other genetic irregularities that can create carcinogenesis. Epigenetics (see Chapter 3, page 62) is the study of changes in organisms (humans included) caused by modification of gene expression (protein production) rather than alteration of the genetic code itself. As with all genetic activity, epigenetics can turn gene expression on or off by the DNA genetic code or by environmental factors. Such abnormalities can produce unpredictable cancers.

4.3. Oncoevolution and p53

Proto-oncogenes are genes that promote cell growth and cellular division, whereas tumor suppressor genes discourage cell growth, or briefly halt the process of DNA repair. A series of many mutations to these proto-oncogenes are needed before a standard cell transforms into a neoplastic cell. This phenomenon is referred to as “oncoevolution.” [15] Tumor suppressor genes that are activated by cellular stress or injury that produce free-floating genetic material can trigger enzymes and pathways that result in the activation of a tumor suppressor gene, p53. This tumor suppression protein arrests the progression of the abnormal cell cycle (apoptosis), preventing mutations from being passed on to subsequent cells [16]. This p53 protein has been named the “guardian of the genome.” In other words, HOORAY for p53!

4.4. Infectious agents

It is estimated that about 20% of cancers are caused by infectious agents [17]. Organisms of the microbiome and its dysbiosis (an imbalance between the types of organisms) can induce carcinogenesis through direct DNA damage and inflammation, indirectly through modulation of immune responses, or by chronic inflammatory responses induced by bacterial metabolites. Among infectious agents, viruses tend to have a higher risk as carcinogens, although bacteria and parasites may also be implicated. Some viruses can disrupt signaling that normally keeps cell growth and proliferation in check. Also, infections can weaken the immune system or cause chronic inflammation that may lead to mutations and subsequent cancers. The most significant viral risks for cancers include the following [18]:

- Epstein–Barr Virus (EBV): Risk of lymphoma and cancers of the nose and throat;
- Hepatitis B Virus and Hepatitis C Virus (HBV and HCV): Risk of

liver cancer;
- Human Immunodeficiency Virus (HIV): Risk of Kaposi sarcoma, lymphomas (including both non-Hodgkins lymphoma and Hodgkins disease), and cancers of the cervix, anus, lung, liver, and throat;
- Human Papillomaviruses (HPVs): Risk of all cervical cancers and penile cancers;
- Human T-Cell Leukemia/Lymphoma Virus Type 1 (HTLV-1): Risk of adult T-cell leukemia/lymphoma (ATLL);
- Merkel Cell Polyomavirus (MCPyV): Risk of Merkel cell carcinoma;
- *Helicobacter pylori* (*H. pylori*): Risk of stomach cancer.

4.5. The microbiome

As mentioned in our previous discussion of infectious agents, it is estimated that individual microbial pathogens contribute to cancer development in approximately 20% of total cases [19]. Among these pathogens, genetic mutations are the main drivers of tumor initiation, with contributions from secondary risk factors like diet, age, lifestyle factors, microbes etc. However, we now know that the microbiome can regulate the effects of tumor-driven mutations and progression through direct effects on the tumor cells and indirectly through manipulation of the immune system. The microbiota may affect tumor immunity by regulating the host immune system and the tumor's microenvironment [20].

Some bacteria help fight tumors by activating immunity, while others mediate immunosuppression to help cancer cells escape from the immune system [21]. The composition of the intestinal microbiota that is sensitive to treatment or prone to adverse reactions can be used as biomarkers to predict the prognosis of immunotherapy and may also assist immunotherapies. The role of the microbiota in regulating not only gut but also systemic immune responses is being studied as to the impact on cancer immunotherapies, particularly with agents targeting the immunologic checkpoints PD-1 and CTLA-4 (discussed previously in Chapters 3 and 5 and later in this chapter).

Efforts are underway to establish the role of each microbe or group of microbes in different kinds of cancers. Physiological responses to immunotherapy, antibiotic, radiation, and chemotherapy in microbes need to be explored. There are numerous immunotherapy strategies being implemented to manipulate multiple immune pathways and molecules. These strategies and increased understanding of the gut microbiomes in immunotherapy has provided significant impact on clinical therapeutics. The immunologic status of the host, tumor invasion status, and biology of malignancies are determining factors for individualized therapy. Additional research on the microbiome will undoubtedly lead to the earlier treatment of various cancers [22].

4.6. X chromosome and microRNA

MicroRNAs (miRNA) are small noncoding RNA molecules that possess enormous regulatory powers. They play key roles in almost all physiological pathways, and more so for our discussion, in the pathogenesis of autoimmune diseases and cancers. Their genomic distribution as previously described in Chapter 3 demonstrates their highest density of sequences on the X chromosome. It is estimated that miRNA regulate up to 50% of all protein-coding genes. Based on "lyonization" or XCI (X chromosome inactivation) described back in Chapter 1, this prodigious, complex embryologic (and evolutionary) genomic process equips females with greater miRNA machinery than males [23]—"for better and for worse" (pardon the pun).

In Chapter 5, we identified ways that XCI and its association with miRNA serve as both phylogeny and ontogeny "paradoxical protection" for the female against certain diseases. But how about mutations, dysregulation, or dysfunction of miRNA biogenesis playing a key role in pathological processes, particularly those of the immune system and oncogenesis? Previous chapters have already demonstrated some of the multiple ways this molecular biologic association contributes to the female predilection for autoimmune diseases as well as cancer risks for both males and females. Now let's consider some additional examples to accentuate the profound influences (and paradoxes) this miRNA and X chromosome amalgam produce.

The female immune system is flexible in its ability to counteract infections and noninfectious diseases, including cancers. This advantage, however, is yet again a paradox of the immune system in that it can result in an increased susceptibility to developing autoimmune diseases as we have described in Chapters 3 and 5. Meanwhile, a significant number of X-linked miRNAs (e.g., miR-221, 222, 98, 532, and more) help in regulating the immune system, but also have oncogenic potential [24]. To add to this complex puzzle, there exist miRNA-dependent, sex-specific clusters like the PD-1/PD-L1 pathway (described below under Therapies) that can both regulate immune responses and provide T-cell cancer immunosurveillance against tumors. Relative to breast cancers, the most common cancer in women, a large patient cohort study identified two circulating X-linked miRNAs (miR-106a–363 and miR-532–502) as promising diagnostic biomarkers [25]. Continued research into this relationship of miRNA and carcinogenesis will lead to the identification of new biomarkers for additional forms of cancer.

5. Clinical presentations in cancers [26]

Cancer embraces a vast number and diversity of diseases that occur in any organ system of the body. The pathological path for cancers is the abnormal proliferation of cells different in type, numbers, and actions of

otherwise normal cells for the tissue or organ system in question. The growth of cells can be rapid or slow. Cell accumulation can be minuscule or massive.

5.1. Diagnosis

The ultimate clinical criteria for a cancer diagnosis are that the cells in question are distinctly different (microscopically and macroscopic) from the ordinary evolution, appearance, and proliferation of cells. Thus, cancer differs from nonneoplastic cellular changes referred to as hypertrophy (increase in the size of cells) and hyperplasia (increase in cell number), where the cells involved are normal in appearance.

When cancer develops, the orderly cellular process breaks down. As cells become more and more abnormal, old or damaged cells survive when they should die, and new cells form when they are not needed. These extra cells can divide without stopping and may form growths called tumors. Many cancers form solid tumors, that are masses of tissue, whereas cancers of the blood, such as leukemias, generally do not form solid tumors. Cancerous tumors are malignant, which means they can spread into, or invade nearby tissues. In addition, as these tumors grow, some cancer cells can break off and travel to distant places in the body through the blood or the lymph system and form new tumors far from the original tumor. A cancer that has spread from the place where it first started (primary site) to another place in the body is called metastatic cancer. The process by which cancer cells spread to other parts of the body is called metastasis. Diagnostic tests ranging from laboratory studies to imaging to biopsy are all clinically indicated in a cancer diagnosis (Table 6.3).

Cancer cells are also often able to evade the immune system, the network of organs, tissues, as well as specialized cells that protect the body from infections and other conditions. Although the immune system normally removes damaged or abnormal cells from the body, some cancer cells are able to “hide” from the immune system (see PDL-1 ligand below). Tumors can also use the adaptive immune system (our “enemy” again) to stay alive and grow. For example, with the help of certain immune system cells that normally prevent a runaway immune response, cancer cells can sometimes prevent the immune system from killing cancer cells (a deadly paradox).

Besides a full examination, including comprehensive family and medical history, the first diagnostic tests in a cancer diagnosis include biopsy and imaging ranging from photography, through nuclear scanning, and MRIs. Other more advanced diagnostic tests include transcriptomics (the study of gene protein expression) and proteomics (the molecular biology of the expressed proteins) to establish diagnostic markers for more accurate diagnoses of cancers. Using global DNA gene expression data derived from epigenetic experiments, genomic sequencing (see Chapter 3, page 55) is now involved in cell type-specific regulation of gene expression. This enables the development of “synthetic promoters” to regulate gene activity

and precisely control protein production.

Table 6.3

- Complete history and physical examination;
- Lab Tests
  - Blood levels for tumor markers produced by cancer cells;
  - Urine, or other body fluids
- Imaging Tests
  - CT Scan
  - MRI
  - PET scan
  - X-rays and Other Radiographic Tests
  - Nuclear Medicine Scans
  - Ultrasound
  - Bone scan
  - Mammograms
- Biopsy
- Endoscopic examination:
  - Bronchoscopy
  - Colonoscopy
  - Cystoscopy
  - Laparoscopy
  - Laryngoscopy
  - Mediastinoscopy
  - Thoracoscopy
  - Upper Endoscopy
- Next-generation sequencing (NGS) oncology assays

Clinical diagnostic tests for cancer.

The tremendous variation in cancer cells, even within the same disease, is one of the greatest challenges in cancer diagnosis. This is being overcome through computerized artificial intelligence (AI) image analysis that can identify different types of cancer cells simply by scanning microscopic images. Results in AI scanning microscopy with image recognition are achieving higher accuracy than previous human judgment. In a dermatological study using 13,000 photographs to identify malignant lesions, a trained AI convoluted neural network (CNN) program yielded higher sensitivity and specificity than a panel of 21 board-certified dermatologists [27].

5.2. Staging [28]

Besides determining the nature and type of cancer in a diagnosis, one of the most critical considerations in the clinical presentation is "staging." This is a determination of how advanced the cancer is relative to its spreading (metastasis) beyond its original location. To determine this, a number is assigned (I through IV) to characterize the degree of spread (from local to disseminated, i.e., to other tissues and/or organ systems beyond the original site). The higher the number, the more cancer has spread locally or throughout the body. This information is critical in determining a plan of treatment.

5.3. Types of cancers

Cancers are identified by the type of cells involved and the area of the body from where they originate. Metastasis relates to the spreading of the cells via blood or lymphatic system from their point of origin to new sites of tumor development. The following terms define the general types of cancers [29,30]

- Carcinoma: cancer that starts in the skin or the tissues that line other organs;
- Sarcoma: a cancer of connective tissues such as bones, muscles, cartilage, and blood vessels;
- Leukemia: cancer of the bone marrow that creates blood cells;
- Lymphoma: cancer that begins in lymphocytes (T cells or B cells):
    - Hodgkins lymphoma—from abnormal B cells (Reed-Sternberg cells);
    - Non-Hodgkin lymphoma—large, rapidly developing group from B cells or T cells.
- Multiple myeloma: cancers that begin in plasma cells and form tumors in bone marrow (also called plasma cell myeloma and Kahler disease).;
- Melanoma: cancer beginning in melanocyte (pigment forming) cells;
- Other tumors:
    - Brain and spinal cord tumors;
    - Germ cell tumors;
    - Neuroendocrine tumors;
    - Carcinoid tumors.

6. Treatment considerations in cancer

The current era of cancer treatments share therapies common to

immunology, genetics, and genomics, many of which have been discussed in Chapters 4 and 5. Used separately and in combination with chemotherapies, radiation therapies, and surgery, the immunotherapies and cellular genetic therapies we've been discussing are being viewed as the hope of future successes in cancer treatments.

6.1. Chemotherapy [31]

Chemotherapy and radiation therapy differ from the immunotherapies and cellular therapies in that the immunotherapies and cellular genetic therapies use the body's own cells (and intrinsic biologic agents) to treat itself. Conversely, chemotherapies utilize biochemical, toxic chemical agents to target and destroy tumor and cancer cells throughout the body. The problem with chemotherapy (and radiation therapy) is their indiscriminate, adverse effects on healthy tissue and organ systems.

Various forms of chemotherapeutic agents effectively disrupt the stages of irregular and rapid cancer cell development. Unfortunately, they are not specific to the cancer cells alone and tend to disrupt normal cell cycles as well, particularly the more susceptible cells of the gastrointestinal tract and hair follicles, thus causing the nausea and hair loss we all hear about and see in cancer patients.

When used with other treatments, chemotherapy can:

- Make a tumor smaller before surgery or radiation therapy. This is called neoadjuvant chemotherapy;
- Destroy cancer cells that may remain after treatment with surgery or radiation therapy. This is called adjuvant chemotherapy;
- Help other treatments work better;
- Kill cancer cells that have returned or spread to other parts of the body.

6.2. Radiation therapy [32]

Radiation therapy targets and attempts to destroy tumors and cancer cells in specific areas of the body by using beams of intense energy to kill the cancer cells. It most often uses X-rays, but protons or other types of energy are now also being used with considerable success. Radiation therapy is delivered by an external beam or by an internal source (usually solid) placed near the tumor. At high doses, radiation kills cancer cells or damages their DNA that causes the cancer cells to stop dividing or die. This process could take days or weeks before DNA is damaged sufficiently to destroy the cancer cells. Subsequently, the cancer cells keep dying for weeks or months after radiation therapy ends. Of course, the risk of damage from an external beam or internal radiation to noncancer cells and tissue is a negative in radiation therapies.

External beam radiation therapy is used to treat many types of cancer.

Brachytherapy is most often used to treat cancers of the head and neck, breast, cervix, prostate, and eye. A systemic radiation therapy called radioactive iodine, or I-131, is most often used to treat certain types of thyroid cancer. Another type of systemic radiation therapy, called targeted radionuclide therapy, is used to treat some patients who have advanced prostate cancer or gastroenteropancreatic neuroendocrine tumors (GEP-NET). This type of treatment may also be referred to as molecular radiotherapy.

6.3. Molecularly targeted therapies

Target therapies for cancer are similar to the immunotherapies that use biologic agents for autoimmune diseases. The agents used differ from chemotherapeutic drugs in that they interfere with specific "molecular targets" that are involved in the growth, and the spread of cancer. Targeted cancer therapies are sometimes called "molecularly targeted therapies" and "precision medicines" by virtue of their target specificity, similar to genetic therapies. As such, they are considered cornerstones in the "precision medicine" concept [33]. Some of the FDA approved target therapies include

- hormone therapies;
- signal transduction inhibitors;
- gene expression modulators;
- apoptosis inducers;
- angiogenesis inhibitors;
- immunotherapies;
- checkpoint inhibitors.

6.4. Monoclonal antibodies

Many monoclonal antibodies (see also Chapter 2, page 39, Chapter 5, page 128 and Table 5.7, page 128) are used to treat cancer. They are a type of targeted cancer therapy [34]. That means they are designed to interact with specific targets. Targeted therapy is the foundation of precision medicine. It is a type of cancer treatment that targets proteins that control how cancer cells grow, divide, and spread. As researchers learn more about the DNA changes and proteins that drive cancer, they are better able to design promising treatments that target these proteins.

Most targeted therapies are either "small-molecule drugs" (molecules small enough to enter cells easily, so they are used for targets that are inside cells) or monoclonal antibodies. Some monoclonal antibodies are also immunotherapeutic because they help turn the immune system against the cancer. For example, some monoclonal antibodies mark cancer cells so that the immune system will better recognize and destroy them. An example is rituximab that binds to a protein called CD20 on B cells and some types of cancer cells, causing the immune system to kill them.

Other monoclonal antibodies called immune checkpoint inhibitors [35] (see Chapter 5, page 130) bring T cells close to cancer cells, helping the immune cells to kill the cancer cells. An example is blinatumomab (Blincyto), that binds to both CD19, a protein found on the surface of leukemia cells, and CD3, a protein on the surface of T cells. This process helps the T cells get close enough to the leukemia cells to respond to and kill them (Fig. 6.1). By the way, I hope you're thinking back to Chapter 1 when I mentioned a bunch of CD receptors which I promised would come back, particularly in the cancer discussion. Promise kept!

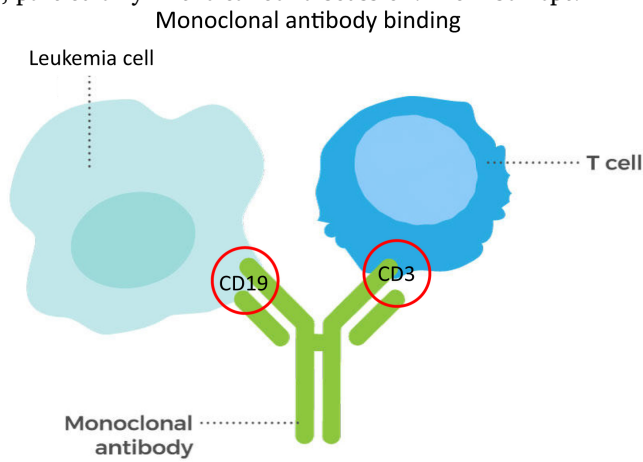


Figure 6.1
Monoclonal antibody binding to C19 and C3 receptors.Monoclonal antibody (blinatumomab [Blincyto]) binding to both CD19, a protein found on the surface of leukemia cells, and CD3, a protein on the surface of T cells. Source: National Cancer Institute, National Institute of Health, U.S. Dept. of Health and Human Services.

6.5. Idiotype-Anti-idiotype Regulatory Circuit (or Loop)

Back in Chapters 2, 4, and 5, I referenced this topic, but kept postponing its full discussion because of its complexity. But now, because of its relevance regarding cancer, we have to take our best shot at describing the "Idiotype-Anti-idiotype Regulatory Circuit (or Loop)" with the goal of "… making it as simple as possible, but not simpler" (*Einstein*). So, here goes.

This complex theory starts with part of an antibody (an "arm" of the "Y" shape of antibodies) binding with a specific antigen. (Easy so far.) Generated B cells (from the T_H cells) begin to produce genetically cloned antibodies with unique profiles of idiotypic epitopes (called idiotypes or antigen-binding sites for the cloned antibodies) that increase immunogenic stimulation through neurotransmitters (chemical bioregulators) [36]. These cloned antibodies begin producing an abundance of B-idiotype cells. These B-idiotype cells generate the set of epitopes (proteins that determine

antigenicity) on the “V” region (from the “Y”) of additional antibody molecules. (The “easy part” didn't last too long, did it?) This stimulation induces antiidiotype and anti-anti-idiotype antibodies (called antibody-2, antibody-3, and beyond) that ultimately suppress continued stimulation by binding with compatible Ts (Treg cells). This binding produces a regulatory closed-loop suppressor system (or circuit) in the lymphoid system [37]. It provides antibodies that can eliminate a persistent antigen, like the carcinogen or carcinogenic stimulus in the case of cancer (Fig. 6.2—Diagram #9: which, by the way, completes the full immune system flow diagram we started back in Chapter 1, Fig. 1.3. How's that for “full circle?”). These antiidiotype antibodies have the potential to provide long-lasting immunity as a vaccine for cancer [38] and COVID-19 [39]. And that's the big takeaway!

This “Idiotype-Anti-idiotype Regulatory Circuit (or Loop),” also referred to as the “idiotype network theory (INT)” was discovered and described by a Danish immunologist, N.K. Jerne, who was awarded the Nobel Prize for medicine in 1984 for his work [40]. But, between you and me, many scientists (myself included) still don't fully understand what it all means (I told you it was complex!). But its potential benefits, especially in future neurotransmitter mitigation therapies in autoimmune diseases [41] (e.g., multiple sclerosis, myasthenia gravis) as well as cancers and COVID-19 vaccine development, to our public health and humanity definitely earn it a place in this discussion. Imagine, a vaccine for cancer? You've gotta wonder what the “anti-vac luddites” will say about that.

6.6. CAAR-T cell therapy or T-cell transfer therapy (gene replacement therapy)

Cancer immunotherapy is a rapidly growing field that has recently demonstrated clinical efficacy in the treatment of solid tumors and hematological malignancies [42]. Up to this point, we have described numerous immunotherapeutic approaches developed to redirect and/or augment immune functions against tumor cells. The application of adoptive cell transfer therapy (ACT therapy – simply the transfer of cells, usually immune cells [autologous – from self or allogenic – from another], with the goal of improving immune function) for the treatment of malignant cancers has now been expanded by the use of T lymphocytes “engineered” to express chimeric antigen receptors (CARs) [43]. As described in Chapter 5, page 137 and Fig. 5.4, chimeric autoantibody receptor T cells (CAAR-T cells) are T cells that have been genetically engineered to give them the new ability to target a specific autoantigen protein. The receptors are “chimeric” because they combine both antigen-binding and T-cell activating functions into a single receptor. Similar to CAAR-T cell therapy, the basis of CAR-T immunotherapy is to modify T cells to recognize, target, and destroy autoantigens as well as cancer cells.

6.7. CAR-T cell therapy

As with CAAR-T cell therapy, CAR-T cell therapy (Fig. 6.3) begins by removing a patient's lymphocytes and transducing them with a DNA plasmid vector (a DNA molecule distinct from the cell's DNA used as a tool to clone, transfer, and manipulate genes or stem cells) that encodes specific tumor antigens. These modified and targeted lymphocytes are then reintroduced into the patient's body (similar to CAAR-T) through a single infusion to attack tumor cells [44]. This treatment has been in used in cancer treatment for more than 25 years, resulting in four generations of improving therapy that has generated effective therapeutic responses for up to 4 years in some studies.

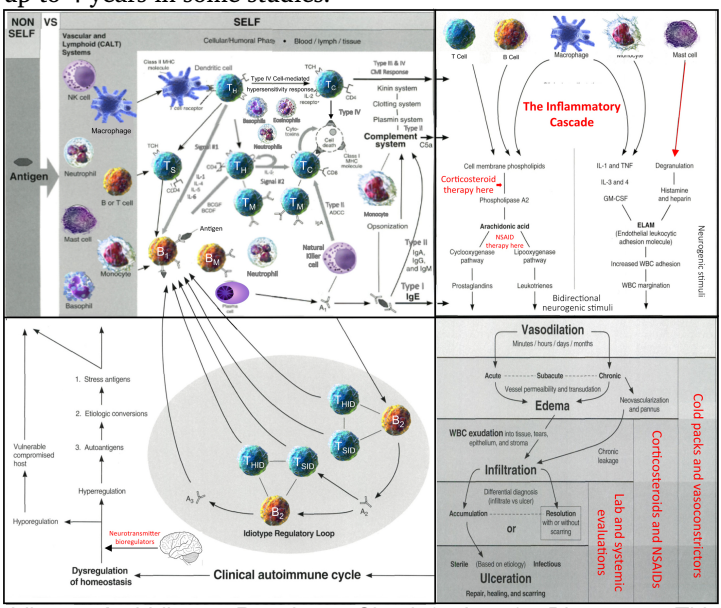


Figure 6.2 Idiotype-Anti-idiotype Regulatory Circuit (or Loop)—Diagram #9.This regulatory closed-loop suppressor system (or circuit) in the immune system provides a multiplication of cloned antibodies (antibody-2, antibody-3, etc.) that can eliminate a persistent antigen, such as the carcinogen or carcinogenic stimulus in the case of cancer (you will note that this figure completes the immune system flow diagram started with the APC diagram back in Chapter 1, Fig. 1.3). Source: Louis J Catania © 2022.

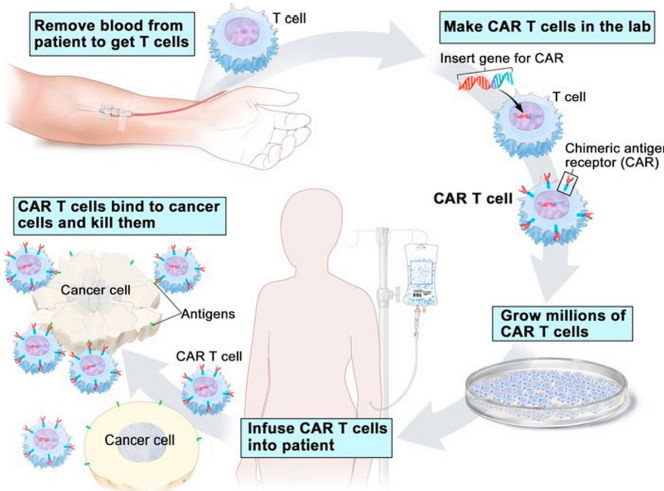


Figure 6.3
Chimeric antigen receptor T-cells (*CART-Ts*).CAR-T-cell therapy begins by removing a patient's lymphocytes and transducing them with a DNA plasmid vector. These modified and targeted lymphocytes are then reintroduced to the patient's body through a single infusion to attack tumor cells. Source: National Institute of Health, U.S. Dept. of Health and Human Services.

There are currently two FDA approved CAR-T products used in cell malignancies [45]. A recent report (February 2022) documented 2 patients with chronic lymphocytic leukemia (CLL) treated with CAR-T therapy 10 years ago remain in remission. This suggests the therapy to be a “cure” (remember how careful we have to be with that word) for CLL [46].

Based upon the high rates of initial cancer remission and durable responses in many patients receiving CAR-T cell therapy, the ACT field has expanded with CAR-T cell therapy now being applied against numerous other B cell-associated antigens with encouraging clinical response data being reported [47]. Again, as previously described about the combination of stem cells with CRISPR-Cas9, so too can CAR-T cell therapies be expanded in combination with CRISPR-Cas9 and stem cell transplantation [48].

6.8. CAR-T cell therapy with CRISPR-Cas9

To increase the efficiency of the CAR-T cells, CRISPR-Cas9 (see CRISPR-Cas9 description in Chapter 5, page 137) has been used to increase their antitumor efficiency by disrupting a programmed death (PD) receptor on the T cell [49]. Cancer cells carry a molecule called a PDL-1 (a ligand, a molecule that binds to another molecule) that binds to PD proteins on a

T cells. This causes the T cell to think (bet you didn't know that T cells think) that the cancer cells are "self" and actually tricks the T cells into protecting the cancer (a little anthropomorphizing to lighten the discussion). The theory is that evolution (there's that 500-million-year thing again) promoted this "pro-cancer" mechanism in our immune defense system to allow a handful of cell mutations (from among the trillions during our lifetime) to survive, produce malignancies and, for lack of a kinder phrase, evolutionarily speaking, "cull the herd." Thanks to immunotherapies, chemotherapies, stem cell transplants, CRISPR-Cas9 and CAR-T cell procedures, we're trying to reverse some of evolution's pernicious efforts. Darwin would not be happy—unless, of course, he was fighting cancer.

6.9. Combination strategies in cancer immunotherapy (immuno-oncology)

Back in Chapter 1, I promised to return to this (yet another) complex topic, but I also promised to be brief. So, let me take a quick shot at making this particular aspect of cancer therapies "as simple as possible, but … yeah, yeah, you know."

Cancer immunotherapy, also known as immuno-oncology, is form of cancer treatment that uses the power of the immune system to treat and hopefully, eliminate cancer. There are numerous forms of immuno-oncology, many of which we have discussed above including targeted antibodies, cancer vaccines, adoptive cell transfer, checkpoint inhibitors, cytokines, biologics, gene therapies, and adjuvants (treatments given in addition to the initial treatment, e.g., surgery, chemotherapy, radiation, or targeted therapies). Combination therapies with certain monoclonal antibodies effecting targeted immune checkpoints have shown considerable promise in cancer therapies.

A research scientist with the MD Anderson Cancer Institute, Jim Allison, Ph.D, yet another immunology Nobel Laureate (2018), invented immune checkpoint blockade immunotherapy which blocks the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on T_C cells (more of that stuff from Chapter 1), freeing these killer immune cells to attack cancers. Blocking the CTLA-4 also liberates T cells to assume new identities, including one that is vital to an effective response against tumors [50]. CTLA-4 and programmed cell death protein 1 (PD-1—see description above), both inhibitory checkpoints commonly seen on activated T-cells have been found to be the most reliable targets for the treatment of cancer. Six drugs targeting PD-1 or its ligand PD-L1 (on the cancer cell) in combination with another drug targeting CTLA-4 have been approved for treatment of different types of cancers and several others are in advanced stages of

development [51]. Did you get all that? Kinda?

The drugs, when administered as monotherapies, showed dramatic increase in their durable response rates and had manageable safety profiles for patients, but more than 50% of patients failed to respond to treatment. Combining a combination of CTLA-4 and PD-1 blockers was then evaluated to increase the response rates in patients, ipilimumab (Yervoy, an anti-CTLA-4) plus nivolumab (Nivolumab [Opdivo], an anti-PD-1). In combination they showed to significantly enhance efficacy in metastatic melanoma patients. Subsequently, ipilimumab plus nivolumab was approved for treatment of metastatic melanoma, advanced renal cell carcinoma, and metastatic colorectal cancer. The success of such "combination strategies" has encouraged multiple clinical studies in other cancer types. The efficacy of combinations has been shown in a number of published studies (some cited below) and more combination therapies are under evaluation in multiple ongoing studies [52].

7. Brief research summaries on cancers

(Reference citations for each research study presented below can be found in the corresponding footnote. Also, a listing of available scientific reference sources and databases used by the author are included in the book's Acknowledgments.)

(There are more literature reviews in this chapter than any other because there is far more research going on in cancer than in any other health-related field, particularly in AI-related research, an area of great interest to *moi*, the author. But you'll also notice in Chapter 7 that COVID-19 research is rapidly catching up.)

1. As research progresses in many areas of cancer, AI continues to be one of the leading technologies being used to advance new information and understandings about the disease. Radiological imaging is one of the more exciting areas of AI's applications because of the strength of its graphic processing unit in analyzing imagery. CNNs (CNNs, AI algorithms) based models have demonstrated accuracies in the 80%–95% range for lung nodule detection and showing significant promise for lung cancer screening. Improvement in breast cancer screening with AI has also been an active area of investigation, resulting in an algorithm able to detect breast malignancy with a sensitivity of 90% [53].
2. In the field of radiogenomics, where radiographic image analysis is used to predict underlying genotypic traits, CNNs are being used with MRI scans to diagnose low-grade gliomas. Additionally, a radiomics signature using extracted features from CT data and a machine learning (ML) algorithm was able to predict underlying CD8 cell tumor infiltration and response to immunotherapy for a variety of advanced cancers. In the area of

translational oncology and complex proteomics data, deep learning (DL) neural networks are being used to predict protein structure, classify cells into a distinct stage of mitosis, and even predict the future lineage of progenitor cells based on microscopy images. In a clinical trial, DL artificial neural networks (ANNs) trained on transcriptomic response signatures to drugs accurately predicted the potential failure of over 200 sample drugs. And another ANN predicted cancer cell sensitivity to therapeutics using a combination of genomic and chemical properties [54].

3. Macrophage cells resist artificial receptors (viral, etc.) and thus, prepare them for cancer immunotherapy applications. Researchers at the University of Pennsylvania not only incorporated CARs with macrophages, they also unleashed their newly acquired firepower to kill tumors in human samples in the lab as well as in humanized mouse models. According to the researchers, their genetically modified macrophages—CAR macrophages—may prove to be especially useful in attacking solid tumors that often leave CAR-T cells exhausted and defeated. Macrophages eat invading cells rather than targeting them for destruction the way T cells do [55]. (See also the recent report regarding CAR-T therapy and leukemia on page 161. Happens to be the same UPenn research group.)
4. Regarding AI's role in cancer treatment, DL algorithms are showing significant value in predicting cancer treatment toxicity. Recently, a CNN approach was used to predict side effects of polypharmacy combinations based on databases of protein–protein and drug–protein interactions. This study led to the discovery of at least five novel drug interaction predictions. The use of AI to predict radiotherapy toxicity has generated significant interest as well over the past few years. Basic neural networks, CNNs, and other ML methods have been explored, using clinical data to predict urinary and rectal toxicity resulting from prostate radiotherapy results, hepatobiliary toxicity after liver radiotherapy, and rectal toxicity for patients receiving radiotherapy for cervical cancer [56].
5. Despite the impressive accuracy DL algorithms provide in cancer research, the unanswered question remains. How did it make its prediction? Currently, the ability to determine the precise logic behind DL-based predictions is lacking. This is often referred to as the “black box” problem. Further work is needed (“explainable AI” [XAI]) to better elucidate the decision-making logic with deep neural networks as AI is positioned to make “disruptive” changes in cancer care. It has shown promise in imaging diagnostics, treatment response evaluation, predicting clinical outcomes, drug development, and translational oncology. Overcoming issues of validation and how algorithms

arrive at their conclusions will be necessary to harness the full potential of AI in cancer diagnosis, treatment, and cures.
A new generation is developing of continuously collected large data sets from various molecular profiling efforts (genetic, genomic, proteomic, epigenomic and others) of patient samples by wearable medical devices (“Internet of Things” or IoTs). Through these method, mobile health applications and clinical outcome data has enabled the biomedical community to apply AI and ML algorithms to vast amounts of data. The application of precision immunoprofiling by image analysis and AI to biology and disease was demonstrated in research papers where the authors used immunoprofiling data to effectively assess immuno-oncology biomarkers, such as PD-L1 and immune cell infiltrates as predictors of patient's response to cancer treatment [57].

6. The interplay between tumor and immune cells within the tumor microenvironment is increasingly important in the study of immuno-oncology. Before DL, algorithms for tissue image analysis were often biologically inspired in collaboration with pathologists and required computer scientists to handcraft descriptive features for a computer to classify a certain type of tissue or cell. ML allows for high-throughput generation of features that describe spatial relationships for thousands of cells, an infeasible task for pathologists. Improvements in individual cell and tissue detection via DL methods allow for very precise measurements of the tumor microenvironment, so heterogeneous features that describe spatial relationships between cells and tissue structures can now be measured at scale [58].
7. Kynurenine pathway enzymes have been identified as key regulators of cancer immunity. An AI with DL technology was employed to rationally design and discover a novel kynurenine pathway regulator with potent immunotherapeutic efficacy. The study demonstrated that AI modeling with DL is a valid strategy for a rational and effective development of an immunotherapeutic drug. This AI-based platform can be applied to other molecular targets to speed up the immuno-oncologic drug development [59].
8. AI technologies are starting to deliver promising results in different fields of aging and longevity research. The most important alterations of aging occur in the adaptive immune system and involve T cells. Many of these alterations are assumed to decrease capacity of the immune system to combat the emerging or progressing tumor. The declining function of the immune system is known as immunosenescence and leads to a higher incidence of infection, cancer, and autoimmune disease-related mortalities in the elderly population [60].

9. Several agents have been shown to induce and increase the immune response in many cancers. Checkpoint inhibitors have revolutionized cancer treatment and their success is mainly due to a durable immune response in cancer. The immune response is patient-specific and thus requires patient-specific treatment. AI can be utilized to predict patient responses and to come up with the right amount of inhibitors to be used. The presence of different immune cells makes the prediction difficult. Scientists have started developing algorithms that can predict immune cell population responses to different inhibitors and how the patient will respond [61].
10. Precision medicine is a valuable method being applied broadly for gaining insights into the genomic profile of tumor Next-generation sequencing (NGS). Simultaneously sequencing millions of DNA fragments in a single sample to detect a wide range of aberrations provides a complete profile of the tumor. The adoption of NGS for clinical purposes has grown tremendously due to the comprehensive detection of aberrations, combined with improvements in reliability, sequencing chemistry, pipeline analysis, data interpretation, and cost.

    NGS supports the discovery of novel biomarkers, including mutation signatures and tumor mutational burden (TMB). Statistical analyses are performed, and patterns are discovered through millions of mutations detected by NGS. It is revolutionizing medical research and enabling multilayer studies that integrate genomic data of high dimensionality such as DNA-seq, RNA-seq. It uses multiomics data such as proteome, epigenome, and microbiome. The integrative analysis of multiomics data provides a better view of biological processes leading to a fuller understanding of these systems compared to single-layer analysis [62].
11. In the field of cancer genomics, the availability of multiomics data, genotype-phenotype data through genome-wide association studies, and literature mining have promoted the development of advanced AI techniques and solutions. This allows medical professionals to deliver personalized care through precision medicine. Precision medicine is a valuable method being applied broadly for gaining insights into the genomic profile of tumor NGS. Simultaneously sequencing millions of DNA fragments in a single sample to detect a wide range of aberrations provides a complete profile of the tumor. The adoption of NGS for clinical purposes has grown tremendously due to the comprehensive detection of aberrations, combined with improvements in reliability, sequencing chemistry, pipeline analysis, data interpretation, and cost. NGS supports the discovery of novel biomarkers, including

mutation signatures and TMB. Statistical analyses are performed, and patterns are discovered through millions of mutations detected by NGS. It is revolutionizing medical research and enabling multilayer studies that integrate genomic data of high dimensionality such as DNA-seq, RNA-seq. It uses multiomics data such as proteome, epigenome, and microbiome. The integrative analysis of multiomics data provides a better view of biological processes leading to a fuller understanding of these systems compared to single-layer analysis [63].

12. Radiologic breast cancer screening has witnessed significant changes along with the successes of DL in the biomedical imaging in general. One such advancement, published in Radiology Journal, was developed by Rodriguez-Ruiz, et al. Authors compared radiologists' performances for reading mammographic examinations unaided versus aided (supported by an AI system) and revealed that radiologists improved their cancer detection performance at mammography when using an AI system. Results also indicated that this benefit was obtained without requiring additional reading time.

    In a complementary study, the data from seven countries was curated by 101 radiologists. This broad experimental setting included a total of 2652 exams, and the stand-alone AI system was statistically similar to that of radiologists' interpretations. The sensitivity and specificity of the system were also found better than the majority of radiologists, but always worse than the best radiologist, which is not surprising. These results indicate that AI tools can be used in much broader settings that have never been used before in breast cancer diagnosis routine. However, for this to be a regular clinical practice, there is still an expectation that more experimentation should be done in both retrospective and prospective settings for independent validations [64].

13. Cancer immunotherapy has made promising strides as a result of improved understanding of biological interactions between tumor cells and the immune system. The recent emergence of quantitative imaging biomarkers provides promising opportunities. Unlike traditional biopsy-based assays that represent only a sample of the tumor, images reflect the entire tumor burden, providing information on each cancer lesion with a single noninvasive examination.

    Computational imaging approaches originating from AI have achieved impressive successes in automatically quantifying radiographic characteristics of tumors. Radiomics-based biomarkers have shown success in different tumor types, but there is no evidence yet in immunotherapy. Tumor morphology, visualized on imaging, is likely influenced by several aspects of tumor biology. Findings suggest associations between radiomics

characteristics and immunotherapy response showing consistent trends across cancer types and anatomical location. Lesions that are more likely to respond to immunotherapy typically tend to present with more heterogeneous morphological profiles with nonuniform density patterns and compact borders [65].

14. Dr. Elizabeth Krakow is using ML to develop precision cancer treatments at the Fred Hutchinson Cancer Research Center in Seattle, WA. Dr. Krakow treats and studies leukemia patients who have relapsed after stem cell transplant. “Past treatments, the current complexity of the disease, side effects—all that info needs to be integrated to intelligently choose the new treatment,” says Krakow. Along with her team Dr. Krakow assembled medical data of 350 relapse patients, 1000 pages per patient. They built a machine-learning algorithm to predict the best treatment sequence for any patient, at any point in time. Her study will enable future work by creating a gold standard that will account for the sequential nature of cancer treatment, which clinical trials have failed to establish [66].
15. Data on cancer stem cell surface molecular markers from 27 of the most common cancer diseases were analyzed using natural language processing and data mining techniques. The source used for the search was 8933 full-text open-access English-language scientific articles available on the Internet. Text mining was based on searching for three entities within one sentence, namely a tumor name, the phrase “cancer stem cells” or its synonym, and a name of a differentiation cluster molecule. As a result, a list of molecular surface markers was formed that included markers most frequently mentioned in the context of certain tumor diseases. This study illustrates the interoperability of AI and ML, through data mining and NLP, to conduct research studies previously not obtainable through standard research protocols [67].
16. BCC is a skin cancer that develops most often on skin areas typically exposed to the sun (UV exposure most common cause —“my bad”), especially the face, ears, neck, scalp, shoulders, and back. It is characterized by an open sore that does not heal, and may bleed, ooze or crust. The sore might persist for weeks, or appear to heal and then come back. Sites are localized and destructive if not treated early. BCC rarely metastasizes and very rarely is fatal. An interesting AI study was conducted at Yale University to develop and validate a multi-parameterized ANN based on available personal health information for early detection of non-malignant skin cancers (NMSC) with high sensitivity and specificity, even in the absence of known UVR exposure and family history. A neural network (NN) was trained on 2056 NMSCs and 460,574 noncancer cases measuring 13 parameters: gender, age, BMI, diabetic status, smoking status,

emphysema, asthma, race-Hispanic ethnicity, hypertension, heart diseases, vigorous exercise habits, and history of stroke. The results (training sensitivity 88.5% and specificity 62.2%, validation sensitivity 86.2% and specificity 62.7%) were comparable to a previous study of basal and squamous cell carcinoma prediction that also included UVR exposure and family history information. These results indicate that an AI NN is robust enough to make predictions, suggesting that novel associations and potential predictive parameters of NMSC [68].

17. A study of colorectal cancer patients was conducted to investigate the effect of an automatic polyp detection system based on DL on polyp detection rate and adenoma detection rate ADR). Of 1058 patients included, 536 were randomized to standard colonoscopy, and 522 were randomized to colonoscopy with computer-aided diagnosis. The AI system significantly increased ADR (29.1% vs. 20.3%, P,0.001) and the mean number of adenomas per patient (0.5 vs. 0.31, P,0.001). Besides, the number of hyperplastic polyps was also significantly increased (114 vs 52, P,0.001). This automatic polyp detection system during colonoscopy resulted in a significant increase in the number of diminutive adenomas detected, as well as an increase in the rate of hyperplastic polyps [69].
18. Scientists have developed a computer method that may help improve the understanding and treatment of Crohn's disease, The study used AI to examine genetic signatures of Crohn's in 111 people. The method revealed previously undiscovered genes linked to the disease and accurately predicted whether thousands of other people had the disease [70].
19. A study was conducted to evaluate DL networks for predicting clinical outcomes by analyzing time-series CT images of patients with locally advanced non–small cell lung cancer. AI DL models using time series scans were significantly predictive of survival and cancer-specific outcomes. This demonstrates that DL can integrate imaging scans at multiple timepoints to improve clinical outcome predictions. AI-based noninvasive radiomics bio-markers can have a significant impact on the clinic given their low cost and minimal requirements for human input [71].
20. A study was conducted to evaluate the applicability of ML methods that combine data on age and prostate-specific antigen levels for predicting prostate cancer. Records of 943 patients who underwent transrectal ultrasonography-guided prostate biopsy were evaluated. A retrospective review of the patients' medical records, analyzed the prediction rate of prostate cancer and identified 20 important features were compared with biopsy results using five different algorithms. Results suggest that the prediction rate of prostate cancer using ML methods may increase the detection rate for prostate cancer and reduce

unnecessary prostate surgery [72].

Chapter highlights (key points and paradoxical-related information)

1. Cancer is not a noun, it's a verb. Cancer is the expression of an irregular mutation of a gene (oncogenesis or "a genetic mistake"). With approximately 25,000 genes in our body mutating constantly, while 99.9% of them (author's approximation) are destroyed by the innate and adaptive immune systems (cellular, humoral, phagocytosis, apoptosis), given the mathematical law of large numbers, it follows that "If you live long enough (or your luck runs out earlier), you'll get cancer." This is the theory of "*cancering.*"
2. Cancers are the second leading cause of death in America, second only to cardiovascular mortality. Unfortunately, COVID-19 has surpassed cancer in 2020 as the leading cause of death in the U.S.
3. Potential causes of oncogenesis (or carcinogenesis) include random genetic mistakes, epigenetics (modified genes), oncoevolution (p53 stimulated), infectious agents, (particularly viruses), the microbiome ("the second genome"), and/or the X chromosome (XCI and microRNA).
4. Types of cancers include carcinomas (soft tissue), sarcomas (connective tissue), leukemias (bone marrow and blood cells), and lymphomas (T and B lymphocytes), multiple myeloma (beginning in plasma cells and form tumors in bone marrow, melanoma (melanocytes), and some less popular miscreants.
5. Metastasis relates to the spreading of the cells via blood or lymphatic system from their point of origin to new sites of tumor development.
6. Cancer presents in "stages" (I though IV) which characterize the degree of spread (from local to disseminated). The higher the number, the more cancer has spread locally or throughout the body.
7. Treatment strategies in cancer include surgery, chemotherapies (utilizing biochemical, toxic chemical agents), and radiation therapies (X-rays and proton beam) that target and destroy tumor and cancer cells. The weakness to these therapies are that they are indiscriminate and adversely affect healthy tissue and organ systems.
8. "Molecular target therapies" for cancer are similar to the

immunotherapies using almost identical biologic agents as used in autoimmune diseases (see Chapters 4 and 5). These agents (e.g., hormones; signal transduction inhibitors; gene expression modulators; apoptosis inducers; angiogenesis inhibitors; and those from Chapter 5) interfere with specific "molecular targets" that are involved in the growth and the spread of cancer.

9. Most targeted therapies are either "small-molecule drugs" (molecules small enough to enter cells), monoclonal antibodies or checkpoint inhibitors.

10. All of the therapeutic strategies mentioned in #7, 8, 9 above are often used effectively as combination therapies (immune-oncology) as well as with the genetic therapies mentioned in Chapters 4, 5, 6 (molecular biology therapeutic procedures ["genetic engineering" or "genetic modification"] including CAR-T and CAAR-T cell [replacement therapy], CRISPR-Cas9 [gene editing], and stem cell therapy [regenerative medicine]).

References

1. Hillis W.D. Edge master class 2010: W. Daniel Hillis on. *Cancer (Phila)* . October 19, 2019 [Edge.org].
2. Anandakrishnan R, Varghese R.T, Kinney N.A, et al. Estimating the number of genetic mutations (hits) required for carcinogenesis based on the distribution of somatic mutations. *PLoS Comput Biol* . 2019;15(3):e1006881.
3. Weinberg R.A. Cancer, mutations, and the facts of life. The Guardian; 2019. weinberg@wi.mit.edu.
4. *American cancer society facts & figures annual report for* . 2018.
5. *Cancer facts & figures* . American Cancer Society; 2019.
6. NCHS Health E-Stats, . *National center for health statistics* . Center for Disease Control (CDC); 2019.
7. Ortaliza J, Orgera K, Twitter K.A, et al. *COVID-19 continues to be a leading cause of death in the U.S. in September 2021* . KFF Health & Wellbeing; October 13, 2021.
8. Siegel R.L, Miller K.D, Jemal A. Cancer statistics, 2020. *ACS J* . January 8, 2020.
9. Global Burden of Disease 2019 Cancer Collaboration. Cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life years for 29 cancer groups from 2010 to 2019: a systematic analysis for the global burden of disease study 2019. *JAMA Oncol* . 2021 Published online December 30.
10. Kuderer N.M, Choueiri T.K, Shah D.P, et al. Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study.

Lancet . 2020;395(10241):1907–1918.
11. Maringe M, Spicer J, Morris M, et al. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. *Lancet Oncol* . 2020;21(8):P1023–P1034.
12. *Genetic disorders* . National Human Genome Research Institute. NIH. USA.gov.; May 18, 2018.
13. Tomasetti C, Li L, Vogelstein B. Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science* . September 22, 2017;355(6331):1330–1334.
14. Belikov A, Aleksey V. The number of critical carcinogenic events can be predicted from cancer incidence. *Sci Rep* . March 23, 2017;7(1):12170.
15. Ibid. Belikov. 14. May 18, 2018. USA.gov.
16. *Genetics home reference. Tumor protein* . NIH. National U.S. Library of Medicine.; October 15, 2019:53. USA.gov.
17. Vande Voorde J, Balzarini J, Liekens S. Mycoplasmas and cancer: focus on nucleoside metabolism. *EXCLI J* . 2014;13:300–322.
18. *Infectious agents* . National Cancer Institute at the National Institutes of Health; 2019.
19. Siegel R.L, Miller K.D, Jemal A. Cancer statistics, 2020. *Ca Cancer J Clin* . 2020;70:7–30.
20. Jain T, Sharma P, Are A.C, Vickers S.M, Dudeja V. New insights into the cancer–microbiome–immune axis: decrypting a decade of discoveries. *Front Immunol* . 2021;12:622064. .
21. Wu M, Bai J, Ma C, Wei J, Du X. The role of gut microbiota in tumor immunotherapy. *J Immunol Res* . August 6, 2021:5061570.
22. Choudhry H. The microbiome and its implications in cancer immunotherapy. *Molecules* . January 3, 2021;26(1):206.
23. Di Palo A, Siniscalchi C, Salerno M, et al. What microRNAs could tell us about the human X chromosome [Published correction appears in Cell Mol Life Sci.;78(8):4067]. *Cell Mol Life Sci* . April 2021;77(20):4069–4080.
24. Johnnidis J.B, Harris M.H, Wheeler R.T, et al. Regulation of progenitor cell proliferation and granulocyte function by microRNA-223. *Nature* . February 28, 2008;451(7182):1125–1129.
25. Zou X, Li M, Huang Z, Zhou X, Liu Q, Xia T, Zhu W. Circulating miR-532-502 cluster derived from chromosome X as biomarkers for diagnosis of breast cancer. *Gene* . January 5, 2020;722:144104.

26. Cancer Overview. *What is cancer staging? Cleveland Clinic* . 2019.
27. Esteva A, Kuprel B, Novoa R.A, et al. Dermatologist-level classification of skin cancer with deep neural networks. *Nature* . 2017;542:115–118.
28. Ibid. Cancer Overview. 26. Cleveland Clinic; 2019.
29. *What do you want to know about cancer?* Healthline; 2019.
30. *Cancer types* . National Cancer Institute of NIH; 2019.
31. *Cancer chemotherapy* . MedLinePlus. NIH. USA.gov.; September 8, 2019.
32. *Radiation therapy* . MedLinePlus. NIH. USA.gov.; September 11, 2019.
33. Genetics Home Reference, . *What are some potential benefits of precision medicine and the Precision Medicine Initiative? NIH* . National U.S. Library of Medicine. USA.gov.; October 15, 2019.
34. *Targeted cancer therapies* . National Cancer Institute. NIH; 23 September 2019.
35. Alteri R, Kalidas M. *Immune checkpoint inhibitors and their side effects* . American Cancer Society; December 27, 2019.
36. Stanova A.K, Ryabkova V.A, Tillib S.V, Utekhin V.J, et al. Anti-idiotypic agonistic antibodies: candidates for the role of universal remedy. *Antibodies* . 2020;9(2):19.
37. Pan S.Y, Chia Y.C, Yee H.R, et al. Immunomodulatory potential of anti-idiotypic antibodies of the treatment of autoimmune disease. *Futur Sci* . October 29, 2020;7(2).
38. Naveed A, Rahman S.U, Arshad M.I, et al. Recapitulation of the anti-Idiotype antibodies as vaccine candidate. *Transl Med Commun* . March 1, 2018;3:1.
39. Naveed A, Naz D, Rahman S.U. Idiotype/anti-idiotype antibodies: as a glorious savior in COVID-19 pandemics. *Transl Med Commun* . 2021;6:18.
40. Kohler H, Pashov A, Kieber-Emmons T. The promise of anti-idiotype revisited. *Front Immunol* . 2019;10:808.
41. Baecher-Allan C, Kaskow B.J, Weiner H.L. Multiple sclerosis: mechanisms and immunotherapy. *Neuron* . February 21, 2018;97(4):742–768.
42. June C.H, O'Connor R.S, Kawalekar O.U, et al. CAR-T cell immunotherapy for human cancer. *Science* . 2018;359:1361–1365.
43. Gill S, June C.H. Going viral: chimeric antigen receptor T-cell therapy for hematological malignancies. *Immunol Rev* . 2015;263:68–89.
44. Wikipedia, . *Plasmids* . September 23, 2019.

45. Porter D.L, Hwang W.-T, Frey N.V, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. *Sci Transl Med* . 2015;7:303ra139.
46. Melenhorst J.J, Chen G.M, Wang M, et al. Decade-long leukaemia remissions with persistence of CD4+ CAR T cells. *Nature* . 2022.
47. Fry T.J, Shah N.N, Orentas R.J, et al. CD22-targeted CAR-T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy. *Nat Med* . 2017;24:20. .
48. Rupp L.J, Schumann K, Roybal K.T, et al. CRISPR/Cas9-mediated PD-1 disruption enhances anti-tumor efficacy of human chimeric antigen receptor T cells. *Sci Rep* . April 7, 2017;7(1):737.
49. Avior Y, Lezmi E, Yanuka D, et al. Modeling developmental and tumorigenic aspects of trilateral retinoblastoma via human embryonic stem cells. *Stem Cell Rep* . 2017;8(D):1354–1365.
50. Leach D.R, Krummel M.F, Allison J.P. Enhancement of antitumor immunity by CTLA-4 blockade. *Science* . March 22, 1996;271(5256):1734–1736.
51. De Silva P, Aiello M, Gu-Trantien C, et al. Targeting CTLA-4 in cancer: is it the ideal companion for PD-1 blockade immunotherapy combinations? *Int J Cancer* . July 2021;149(1):31–41.
52. Mokhtari R.B, Sambi M, Qorri B, et al. The next-generation of combination cancer immunotherapy: epigenetic immunomodulators transmogrify immune training to enhance immunotherapy. *Cancers* . 2021;13(14):3596.
53. McKinney S.M, Sieniek M, Godbole V, et al. International evaluation of an AI system for breast cancer screening. *Nature* . 2020;577:89–94.
54. Sun R, Limkin E.J, Vakalopoulou M, et al. A radiomics approach to assess tumor-infiltrating CD8 cells and response to anti-PD-1 or anti-PD-L1 immunotherapy: an imaging biomarker, retrospective multicohort study. *Lancet Oncol* . 2018;19:118091.
55. Klichinsky M, Ruella M, Shestova O, et al. Human chimeric antigen receptor macrophages for cancer immunotherapy. *Nat Biotechnol* . 2020;38:947–953.
56. Ibragimov B, Toesca D, Chang D, et al. Development of deep neural network for individualized hepatobiliary toxicity prediction after liver SBRT. *Med Phys* . 2018;45:4763–4774.
57. Tjoa E, Guan C. *A survey on explainable artificial intelligence (XAI): towards medical XAI* . Cornell University; October 15,

2019 arXiv:1907.07374 [cs.LG].
58. Vamathevan J, Clark D, Czodrowski P, et al. Applications of machine learning in drug discovery and development. *Nat Rev Drug Discov* . 2019;18(6):463–477.
59. Lee W.S, Kim J.H, Lee H.J, et al. Artificial intelligence technology enables a rational development of a potent immunotherapeutic agent. In: *Proceedings of the annual meeting of the American Association for Cancer Research* . vol. 80. Philadelphia (PA): AACR; June 22, 2020 (16 Suppl. l): Abstract nr 2092.
60. Pawelec G. Age and immunity: what is “immunosenescence”. *Exp Gerontol* . 2018;105:4–9.
61. Poleszczuk J, Enderling H. The optimal radiation dose to induce robust systemic anti-tumor immunity. *Int J Mol Sci* . 2018;19.
62. Steuer C.E, Ramalingam S.S. Tumor mutation burden: leading immunotherapy to the era of precision medicine? 2017. *J Clin Oncol* . 2018;36:631–632 Available from:. https://doi.org/10.1200/JCO.76.8770.
63. Pennell N.A, Mutebi A, Zhou Z.Y. *Economic impact of next generation sequencing vs sequential single gene testing modalities to detect genomic alterations in metastatic non-small cell lung cancer using a decision analytic model* . ASCO; 2018.
64. Rodríguez-Ruiz A, Krupinski E, Mordang J.J, et al. Detection of breast cancer with mammography: effect of an artificial intelligence support system. *Radiology* . 2019;290:30514.
65. Trebeschi S, Drago S.G, Birkbak N.J, et al. Predicting response to cancer immunotherapy using noninvasive radiomic biomarkers. *Ann Oncol* . 2019;30(6):9981004.
66. Keown S. *Using algorithms to personalize patient care* Dr. Elizabeth Krakow, a blood-cancer specialist, and epidemiologist. Fred Hutch News Service; October 1, 2018.
67. SuvorovYa R.E, Kim S.A, Gisina M, et al. Surface molecular markers of cancer stem cells: computation analysis of full-text scientific articles. *Bull Exp Biol Med* . 2018;166(1):13540. .
68. Roffman D, Hart G, Girardi M, et al. Predicting non-melanoma skin cancer via a multi-parameterized artificial neural network. *Sci Rep* . 2018;8(1):1701 Available from:. https://doi.org/10.1038/s41598-018-19907-9.
69. Wang P, Berzin T.M, Romek J, et al. Real-time automatic detection system increases colonoscopic polyp and adenoma detection rates: a prospective randomized controlled study. *BMJ* . 2019;68(10).
70. Wang Y, Miller M, Astrakhan Y, et al. Identifying Crohn's

disease signal from various analyses. *Genome Med* . 2019;11(1).
71. Xu Y, Hosny A, Zeleznik R, et al. Deep learning predicts lung cancer treatment response from serial medical imaging. *Clin Cancer Res* . 2019.
72. Lee J, Yang S.W, Lee S, et al. Machine learning approaches for the prediction of prostate cancer according to age and the prostate-specific antigen level. *Korean J Urol Oncol* . 2019;17.

7: Immunology

The science of pandemics, infectious disease and COVID-19

Abstract

The novel coronavirus, Severe Acute Respiratory Syndrome (SARS)-CoV-2 originating in the City of Wuhan, China in December 2019 and spread rapidly throughout China (an epidemic). Within 2months, it had spread throughout the entire world becoming the pandemic labeled COVID-19. As this chapter is being written (early 2021), this devastating disease remains uncontrolled, causing countless and tragic death worldwide. The life cycle of the virus including its spike protein and affinity to ACE-2 receptors is well understood, but notwithstanding vaccines (Pfizer and Moderna mRNA), antiviral drugs, and monoclonal antibodies just being FDA approved (emergency use authorization—EAU), this highly contagious agent continues to spread. Only classic public health preventive measures like isolation, social distancing, masks, and copious handwashing are effective, yet difficult to enforce with people and politics in open societies. As with any pandemic, unless herd immunity is achieved through an effective immunization program, identifying infected individuals is critical. Antigen tests (polymerase chain reaction) detect active viral infection while antibody tests identify previously infected people who might be considered henceforth immune (though inconclusive with SARS-CoV2). Perhaps the most valuable information on the disease is coming from the enormous body of AI assisted research of which this chapter addresses.

Keywords

ACE-2; Artificial intelligence (AI); Coronavirus; COVID-19; Herd immunity; Monoclonal antibodies; mRNA; Pandemic; Polymerase chain reaction (PCR); SARS-CoV-2; Spike protein; Vaccine

> *The secret of change is to focus all of your energy, not on fighting the old, but on building the new.*
>
> *Socrates*

1. Introduction

This chapter is being written early in the year 2021. As we are all

painfully aware, the world was struck by a virulent and highly contagious form of a coronavirus, referred to as the “novel coronavirus” or SARS-CoV-2 at the end of 2019. During the months that followed, this (Severe Acute Respiratory Syndrome [SARS]-CoV-2) virus spread to create a global pandemic referred to as COVID-19. It's a fortuitous coincidence that this book is being written during an infectious pandemic and published as the pandemic slowly (hopefully) regresses. Along with the associated bioscience, epidemiology, and public health issues regarding COVID-19, its most intimate relationship with science is with immunology. It is without question the most relevant science addressing such a pernicious disease and the biomedical, emotional, and mental trauma it effectuates.

It's sad that any book (or chapter) related to something as calamitous as a worldwide, infectious pandemic needs be written at all. The coincidence, however, of such a book chapter written at a time that can enlighten readers to the profound relationship immunology brings to this human tragedy can't be overstated. It must be regarded as an opportunity to provide humankind with yet a further understanding of “the paradox of the immune system.” Its negative effects as “an enemy and villain” produces clinical dilemmas, yet its applications as “our friend” gives us a greater understanding of the virus and leads to the development of vaccines to provide remedies and hope. Indeed, immunology will help us restore our personal well-being and worldwide public health.

A reasonable understanding of a ubiquitous and “novel” viral infectious disease, the nature of COVID-19 requires first a brief historical background on contagious infections and pandemics. Then we will address the pathogenesis of viral infections and specifically, the immunologic and immunogenic mechanisms and theories of SARS-CoV-2, followed by the clinical diagnostic and therapeutic considerations of coronavirus infections. Finally, we will present and address the profound epidemiologic and public health implications associated with the COVID-19 global pandemic. Notwithstanding it being a fraction of the body of literature already published on the topic, throughout this Chapter and at the end, we will include reviews and research from the ever-growing body of literature that is helping us better understand and hopefully, eventually control this viral infectious pandemic and those that inevitably will follow.

Much of the discussion in this chapter will have direct relationships to the immunology and genetic information presented in previous chapters in this book. The 2 greatest strengths I feel this Chapter brings to the reader as compared to other COVID-19 literature are: (1) it provides an organized summary of all the important and valuable information (to date) you need to know regarding the immunology of the coronavirus, infectious pandemics, and COVID-19 specifically; and (2) and perhaps its greatest value is that the collective chapters of the book provide immediate access to the most valuable, relevant immunological information regarding COVID-19 for quick reference. This relevant information (and its

companion glossary of terms, not readily available in many books or in most articles) provides a fuller understanding of this critical subject for readers with backgrounds at any level of science, immunology, or medical experience.

Finally, I dedicated this book with my deepest sympathy to those souls lost during this COVID-19 pandemic, to their families, and to all those in health care and their families who have sacrificed so much. Sometimes words of appreciation fall short when there is so much suffering. But all I can hope is that, in some small way, personally or professionally, this literary contribution might help some of the heroes from this pandemic who made such unselfish sacrifices. I sincerely thank them all.

2. Background considerations

2.1. Definitions

An endemic level of disease can be defined as that level of observable disease found in a community and considered a baseline or expected level. Occasionally, the expected level of disease may rise, often suddenly, in a defined geographic area and is termed an “outbreak.” If the rise in the cases is grouped in a specific place, it is considered a “cluster,” but if they are broadly distributed, it is considered an “epidemic.” Finally, a pandemic refers to an epidemic that has spread over several countries or continents, usually affecting large numbers of people (sound familiar?) [1].

Epidemics and pandemics occur when an infectious agent (e.g., a virus) is sufficiently virulent and contagious enough to be conveyed to a large number of susceptible hosts (humans). These conditions may result from:

- A recent increase in amount or virulence of the agent;
- The recent introduction of the agent into a setting where it has not been before;
- An enhanced mode of transmission so that more susceptible persons are exposed;
- A change in the susceptibility of the host response to the agent; and/or
- Factors that increase host exposure or involve introduction through new portals of entry.

2.2. History of pandemics

2.2.1. Historical overview

Outbreaks of infectious disease have shaped the economic, political, and social aspects of human civilization, their effects often lasting for centuries. These outbreaks have defined some of the basic tenets of modern medicine with the development of the principles of epidemiology, prevention, immunization, and the field of public health. Throughout history, pandemic outbreaks have decimated societies, determined outcomes of wars, and wiped out entire populations. Yet paradoxically,

they have ushered in new innovations, created and advanced sciences including medicine, immunology, genetics, and public health, as well as fields of economics and political science systems.

The best-known examples of recorded plagues are those referred to in religious writings starting with the Old Testament. The Athenian plague is an historically documented event that occurred in 430–26 B.C. during the Peloponnesian War. This plague affected a majority of the inhabitants of the overcrowded city-state and claimed lives of more than 25% of the population. Subsequent plagues over the centuries affected the Roman Empire (the Antonine plague), the Justinian plague, and forward to 13th century and the Black Plague, a global outbreak of the bubonic plague that originated in China in 1334, arrived in Europe in 1347, and over the following 50 years it reduced the global population from 450 million to possibly below 300 million. Some estimates claim that the Black Death claimed up to 60% of lives in Europe at that time [2].

2.2.2. Recent history

Three influenza pandemics occurred at intervals of several decades during the 20th century, the most severe of which was the so-called “Spanish Flu” (caused by an A[H1N1] virus), estimated to have caused 20 to 50 million deaths in 1918–19. Milder pandemics occurred subsequently in 1957–58 (the “Asian Flu” caused by an A[H2N2] virus) and in 1968 (the “Hong Kong Flu” also caused by an A[H3N2] virus), that were estimated to have caused one to four million deaths each.

Polio (classified as an epidemic) occurred in the United States from 1916 to its peak in 1952. Of the 57,628 reported cases, there were 3145 deaths. Dr. Jonas Salk developed a vaccine and in 1962, the average number of cases dropped to 910. The Centers for Disease Control and Prevention (CDC) Trusted Source reports that the United States has been polio-free since 1979. Unfortunately, there have been recent reports of new cases of polio developing in industrialized and developing countries [3].

The first influenza pandemic of the 21st century occurred in 2009–10 and was caused by an influenza A(H1N1) virus. This H1N1 pandemic was a reprise of the “Spanish flu” pandemic from 1918, but with far fewer devastating consequences. Suspected as a reassortment of bird, swine, and human flu viruses, it was coined the “swine flu.” For the first time, a pandemic vaccine was developed, produced, and deployed in multiple countries during the first year of the pandemic. While most cases of pandemic H1N1 were mild, globally it is estimated that this 2009 pandemic caused between 100,000 and 400,000 deaths in the first year alone. Other prominent epidemics and pandemics that occurred in the early 21st century included Ebola, Lassa fever, Middle East respiratory syndrome coronavirus (MERS-CoV), Nipah and henipa viral diseases, Zika, and others.

The first outbreak of SARS was at the start of the 21st century. It was

caused by the SARS Corona virus (SARS-CoV-1) and started in China. It affected fewer than 10,000 individuals, mainly in China and Hong Kong, but also in other countries, including 251 cases in Canada (Toronto). The severity of respiratory symptoms and mortality rate of about 10% caused a global public health concern. Through the vigilance of public health systems worldwide, the outbreak was contained by mid-2003. This certainly is a sad statement when considering the virtually uncontrolled evolution and spread of the SARS-CoV-2 pandemic being experienced during the second decade of the 21st century. How can we have let it happen? The novel coronavirus (SARS-CoV-2), being more contagious than the SARS-CoV-1, was allowed to spread uncontrolled because of inadequate attention (personal responsibility and political accountability—*aka* "total insanity!") to the simplest cardinal rules of public health to controlling infectious disease, that is, testing, quarantine, social distancing, copious hygiene (hand-washing), wearing masks, and contact tracing. Such a sad statement has resulted in otherwise avoidable, unimaginable human suffering [4].

2.3. HIV and AIDs [5]

Among the most serious pandemics of the 20th and 21st century is (note the use of the present tense) the human immunosuppressive virus (HIV) first documented in 1981. The pandemic first appeared to be a rare lung infection originating in Africa. Now it is known that it damages the body's immune system and compromises its ability to fight off infections. Acquired immune deficiency syndrome (AIDS) is the final stage of HIV and the sixth leading cause of death in the United States among people 25–44 years old. While no cure currently exists, treatments (antiretroviral therapy [ART]) have been developed and the number of deaths has fallen to 19% since 2005.

Second only to COVID-19, HIV is considered one of the world's most serious health and development challenges since the first cases were reported in 1981. As of 2020, approximately 76 million people have become infected with HIV since the start of the epidemic. There are approximately 38 million people currently living with HIV, and 10s of millions of people have died of AIDS-related causes since the beginning of the epidemic. Considered an epidemic in the U.S., its worldwide distribution qualifies it as a pandemic as well. Whatever the case, stop and consider what these facts lay bare. In the year 2021, we are living with two active pandemics and no less than four in the past two decades. Biologists estimate that 380 trillion (10^{38}) viruses are living on our planet, land and sea, and inside our bodies right now—10 times the number of bacteria [6]. Given that fact, it doesn't take much imagination to realize that we will be living with infectious pandemics for a long, long time. Such a thought raises the Santayana adage that "those who do not remember the past are condemned to repeat it." We can only hope that the science skeptics (and no less the climate crisis deniers) finally wake up and

help us shape a future for our children, their children, and for all humanity.

2.3.1. The human immunodeficiency virus (HIV)

HIV is a virus that attacks the T_H (or CD4) cells that help the body fight infection, making a person more vulnerable to other infections and diseases. It is spread by contact with certain bodily fluids of a person with HIV, most commonly during unprotected sex (sex without a condom or HIV medicine to prevent or treat HIV), or through sharing injection drug equipment. As with other viruses, the human body can't get rid of HIV and no effective HIV cure exists. So, once you have HIV, you have it for life. However, by taking HIV medicine like ART [7], people with HIV can live long and healthy lives and prevent transmitting HIV to their sexual partners. In addition, there are effective methods to prevent getting HIV through sex or drug use, including preexposure prophylaxis and postexposure prophylaxis.

2.3.2. Acquired immunodeficiency syndrome

If left untreated, HIV can lead to the disease AIDS (*acquired immunodeficiency syndrome*). AIDS is the late stage of HIV infection that occurs when the body's immune system is badly damaged because of the virus. In the U.S., most people with HIV do not develop AIDS because taking HIV medicine every day as prescribed stops the progression of the disease.

A person with HIV is considered to have progressed to AIDS when [8]

- the number of their CD4 cells falls below 200 cells per cubic millimeter of blood (200 cells/mm3). (In someone with a healthy immune system, CD4 counts are between 500 and 1600 cells/mm3.) or
- they develop one or more opportunistic infections regardless of their CD4 count.

Without HIV medicine, people with AIDS typically survive about 3 years. Once someone has a dangerous opportunistic illness, life expectancy without treatment falls to about 1 year. HIV medicine (ART) can still help people at this stage of HIV infection, and it can even be lifesaving. People who start ART soon after they get HIV experience more benefits, that's why HIV testing is so important.

3. Incidence and prevalence of COVID-19

Originating in the City of Wuhan, China in December 2019, the novel coronavirus spread rapidly throughout China (epidemic) and within 2 months, it had spread throughout the entire world becoming a pandemic labeled COVID-19. At the time of this writing (early 2021), this pandemic

had spread to 213 countries and territories and has escalated to greater than 112 million reported cases and greater than 2.5 million deaths worldwide. In the United States, the rate of infection is greater than 28.6 million cases or 25.5% of the worldwide total and greater than 508,000 deaths or 20.3% of the world's total (statistics as of March 2021 [9,10]). Unfortunately, I anticipate that readers of this chapter will look back upon these numbers and their escalation as a regrettable measure of the lack of compliance with the necessary public health concurrence.

In the United States, COVID-19 has already become the number three leading cause of death in 2020, just behind heart disease and cancer. *(As stated in Chapter 6 , during final proofing of this manuscript [late 2021], new report indicated that statistic having grown to over 700,000 deaths making it the leading cause of death in the U.S, How sad to have ever let that happen [11])*. During the pandemic, the CDC reported that life expectancy dropped by at least a full year during the first half of 2020 (men saw a drop of 1.2 to 75.1 years, while women saw a decrease of 0.9 years to 80.5), the greatest drop since World War II and COVID-19 mortality rate more than doubled over the subsequent 12-month period. There is little doubt that when you read this book, these case numbers and mortality rates will have grown substantially, hopefully less than currently predicted. However, as improved viral controls (i.e., vaccines and antiviral drugs) become more available (a good thing), there seems to be an ominous increase in “super spreader” events (a bad thing) worldwide with large crowd gatherings in close proximity, not wearing masks, as well as some governments (state and national) disregarding necessary restrictions. Such ignorance of the need for public health preventive measures can only lead to increased disaster. (It's just so frustrating to see the politicization of such a public health crisis.)

3.1. Viral mutations

Mutations are the changes in the structure of the DNA or RNA of a gene, resulting in a variant form of the genome that may be transmitted to subsequent generations. Most microorganisms are based on a DNA genome. Some viruses, including the coronavirus, have RNA-based genomes instead. In general, viral RNA genomes are much more mutation-prone than those based of DNA. This distinction is important because RNA-based viral mutations have a greater potential for increased virulence, greater transmissibility, and worst of all, producing a resistance to drugs. So oftentimes, a vaccine developed for a particular viral genome becomes ineffective for its mutated variant. Such is the concerns with the variants developing in the SARS-CoV-2 virus.

As the prevalence of coronavirus increases across the planet, there is concern for any factors that might increase the transmissibility and severity of infection. Different variants are evolving from “mutations” of the viral genome. Evidence of this has been discovered in a number of countries (UK, South Africa, Brazil, and the U.S.) so far. The CDC

described a variant strain of SARS-CoV-2 that was discovered in parts of the UK (specifically the South East), that accounted for 60% of infections in London. Studies have shown that some variants spread more quickly than others. The 614G sequence variant demonstrates a mutation in the virus's spike protein (more on this below), representing a potential risk of worsening the pandemic. Other variants have been associated with higher rates of infectivity (e.g., the delta variant and a rapidly evolving omicron variant).

Public Health of England has said there is no evidence new variants tested are resistant to the Pfizer-BioNTech vaccine, that is now being given across the country to high-priority groups such as healthcare workers. Nor is there any indication at this point of increased infection severity associated with the new variants (although this is being refuted now in more studies in multiple countries). A new South African variant (omicron) identified in the United Kingdom is considered completely different from the UK variants and seems to spread more easily and quickly than other variants discovered so far. The CDC announced in November 2020 that it had launched the National SARS-CoV Strain Surveillance (NS3) program to help track the viruses undergoing mutation characterization. The CDC stated that there is currently no evidence that the variants discovered so far that can cause more severe illness or increased risk for death.

4. Pathogenesis, immunologic, and immunogenic considerations for SARS-CoV-2

4.1. Mechanisms

Viruses are not living cells or organisms. They are obligate parasites or nonliving organisms that lack metabolic machinery of their own to generate energy or to synthesize proteins. Rather, they require a living host to exploit or infect (enter) so they can replicate to complete their life cycle (see Fig. 7.1 and Life Cycle below). The invading virus uses either its genomic DNA or RNA to replicate in the host cell. Coronaviruses (CoV) are a family of RNA viruses that typically cause mild respiratory disease in humans. They include MERS-CoV and SARS-CoV-1, thought to be driven by the spillover of bat-adapted CoVs into an intermediate host (see below). The novel coronavirus (SARS-CoV-2) is a single positive-strand RNA virus that is the largest genome known. Thus, these viruses are poorly adapted to the human host and if transmitted to humans (e.g., SARS-CoV-2), they are generally associated with more severe clinical presentations. Also, if infection occurs (and subsequent mutations), it can be highly transmissible from person to person as SARS-CoV-2 has demonstrated [12].

Coronavirus disease leads to fast activation of innate immune cells, especially in patients developing severe disease. Innate immune activation, levels of many proinflammatory effector cytokines (e.g., TNF, IL-1b, IL-6, IL-8, G-CSF [granulocyte colony-stimulating factor] and GM-CSF

[granulocyte-macrophage colony-stimulating factor]), as well as higher levels of chemokines (e.g., MCP1, IP10, and MIP1α) are also found in those who are critically ill. The levels of some T cell-derived cytokines (e.g., IL-17) are also increased. Often with these cytokines, a "cytokine storm" develops that triggers a hyperinflammatory state. As stated above and in Chapter 4 on chronic inflammation (the progenitor of *all* disease), this inflammatory clinical response leaves virtually all organ systems vulnerable to adverse effects from the novel coronavirus [13]. Of increasing concern are the cardiovascular effects resulting from perivasculitis (inflammation of the adventitia and endothelial lining of blood vessel walls—see Chapter 4, page 76). Antiinflammatories (corticosteroids) and cytokine inhibitor drugs (e.g., checkpoint inhibitors, IgG, Interleukin six blockers) are being studied and beginning to show some benefits in advanced cases and late-stage disease [14].

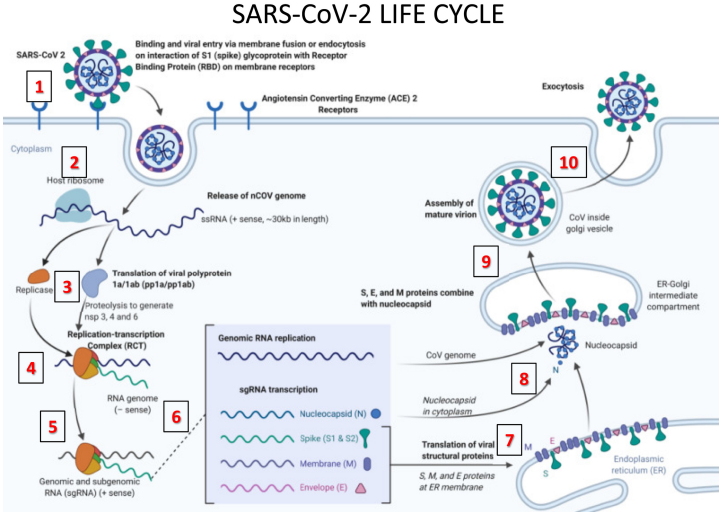


Figure 7.1 SARS-CoV-2 life cycle.The life cycle of the novel coronavirus (SARS-CoV-2) begins when its spike protein attaches to an ACE2 receptor on a cell membrane (1) and penetrates the cell wall where it replicates a genomic RNA (2–4), then produces "subgenomic RNAs" (5–6), synthesizes various spike proteins through translation (7) and new genomic RNA becomes the genome of a new virus particle (8). This combines with the strand genomic RNA, merges in the endoplasmic reticulum-Golgi apparatus into a complete virus particle within a vesicle (9), and the new viral particles are released (exocytosis) to the extracellular region (10). Shereen MA, Khana S, Kazmi A, et al. COVID-19 infection.

4.2. Life cycle of SARS-CoV-2

The pathogenesis and life cycle of SARS-CoV-2 includes a complex of RNA genomic transfers and regenerations to produce the proliferation of the virus. The extracellular and intracellular (host cytoplasm) process involved is illustrated in Fig. 7.1 and traced through the following steps. I think you

will be able to follow the “bouncing ball” through this life cycle and the illustration may (or may not) help. If you're completely flummoxed by the whole thing, don't worry. Just wear your mask, get vaccinated and you'll never need to know the difference between a nonstructural protein from a ham sandwich (rich in protein, I might add).

1. When the spike protein of SARS-CoV-2 binds to the ACE-2 receptor (described below) of the host cell, the virus enters the cell;
2. Then, the fatty envelope of the virus is peeled off by the host ribosome that releases the viral genomic RNA into the cytoplasm of the cell;
3. The ORF1a and ORF1b (genes) RNAs are produced by genomic RNA and then translated into pp1a and pp1b proteins, respectively;
4. Protein pp1a and ppa1b are cleaved by protease (proteolysis) to make a total of 16 nonstructural proteins;
5. Some of the nonstructural proteins form a replication/ transcription complex (RNA-dependent RNA polymerase, RdRp), that use the (+) strand genomic RNA as a template (see Chapter 3, page 51 for transcription and translation explanation);
6. The (+) strand genomic RNA produced through the replication process becomes the genome of a new viral particle;
7. Subgenomic RNAs produced through transcription are translated into structural proteins (in the diagram: S: spike protein, E: envelope protein, M: membrane protein, and N: nucleocapsid protein) that form a viral particle;
8. Spike, envelope, and membrane proteins enter the endoplasmic reticulum of the cell, and the nucleocapsid protein is combined with the (+) strand genomic RNA to become a nucleoprotein complex;
9. This complex merges into the complete virus particle in the endoplasmic reticulum-Golgi apparatus compartment; and
10. The new viral particles are released (exocytosis) to extracellular regions through the Golgi apparatus and the vesicle.

(Chapter 3 may have aided in your understanding of this step-by-step life cycle explanation and may have added to your genomic knowledge base. If you got even half of all that, you're way ahead of 99% of the world's population.)

4.3. Theories

Several studies suggest that antibodies against non-SARS-CoVs are highly prevalent in the general population including children, suggesting that many or most individuals have been infected by CoVs in the past and have potentially developed a certain degree of (protective) immune response

[15]. The severity and the clinical picture in many patients could even be related to the activation of an exaggerated immune mechanism ("cytokine storm"), causing uncontrolled inflammation, akin to autoimmune disease (i.e., the immune system as "Enemy #2"). The hypothesis that SARS-CoV-1 (or other, antigenically similar CoV-1) has silently infected a significant proportion of the population, inducing "herd immunity" (see "Treatment and management strategies" below) needs to be confirmed. Indeed, immunity against the infection, or patterns of semiimmunity (capacity of the immune system to avoid severe infection) may be due to cellular immunity rather than proinflammatory humoral immune responses [16]. Animal models suggest that the efficiency of T lymphocyte-mediated immune responses (see Chapter 2, page 31) is also pivotal for controlling SARS-CoV infections [16]. (Lots of stuff from Chapters 1 and 2 resurfacing here.)

Within 19 days after symptom onset, a total of 100% of 285 patients with COVID-19 tested positive for antiviral immunoglobulin-G (IgG). Seroconversion for IgG and IgM (transition of the test results for IgG or IgM against SARS-CoV-2 from negative to positive results in sequential samples) occurred simultaneously or sequentially. Both IgG and IgM titers plateaued within 6 days after seroconversion [17]. Thus, serological testing may be helpful for the diagnosis of suspected patients with negative reverse-transcriptase–polymerase-chain-reaction (RT–PCR) (an antigen diagnostic test—see below) results and for the identification of asymptomatic infections.

There is currently no data on the specific role of either humoral or cellular immunity or innate immunity in patients recovering from COVID-19. T lymphocytes responsible for clinically relevant antiviral immune responses have a significant chance to be locally present in, or close to, respiratory epithelia. It is very possible that the exclusive detection of humoral immunity against SARS-CoV-2 leads to an underestimation of the anti-SARS-CoV-2 immune responses. It becomes plausible that, after infection by SARS-CoV-2, a sort of race decides the course of the events. Either a cellular innate immune response rapidly clears SARS-CoV-2 without any (or mild) clinical signs of infection or the virus causes a state of immunosuppression that debilitates and sometimes overwhelms the host's (human) defense [18].

4.4. Natural pathogenesis (theorized)

Researchers have analyzed genomic data related to the overall molecular structure of the new coronavirus. Their testing has traced this novel coronavirus to a strain of Malaysian anteater (pangolin) containing genomic regions that are very closely related to the human virus. Their analysis showed that the genome resembles that of a bat coronavirus discovered after the COVID-19 pandemic began. However, in "SARS-CoV-2 testing," the binding region of the spike protein resembles the novel virus found in pangolins (anteaters). This provides additional evidence that the

coronavirus that causes COVID-19 almost certainly originated in nature, most likely in bats [19] with an intermediate animal (anteater or monkey?) host and ultimately transmitted to humans ("zoonotic spillover") [20]. This genetic information concludes that "coronaviruses clearly have the capacity to jump species boundaries and adapt to new hosts" (virus recently reported in Malaysian tigers in Bronx Zoo [21]). This information makes it predictable that more will emerge in the future. This phenomenon could be a serious ongoing treat when considering the reverse, human to animal (anthroponotic) transmission that is now being reported with increased frequency. Reports include common pets (including dogs and cats) though rare, multiple species, and familial primate species (homids) that interact with humans in zoos (gorillas, orangutans, chimpanzees, and bonobos) [22].

Most important among these findings is the receptor binding domain (spike protein) that dictates how the virus is able to attach and infect human cells (see Life cycle above). This comparative analysis of genomic data dispelled the postulate that the virus was laboratory constructed or was a "manipulated" virus. Rather, it promotes a lesson learned to reduce human exposure to wildlife and to ban the trade and consumption (e.g., "wet markets" in China) of wildlife. However, as not all of the early COVID-19 cases were wet market associated, it is possible that the emerging story is more complicated than first suspected.

4.5. Genetic and genomic considerations

The genomic data of the new coronavirus responsible for COVID-19 show that its spike protein contains some unique adaptations. One of these adaptations provides special ability of this coronavirus to bind to a specific protein on human cells called angiotensin converting enzyme (ACE-2) [23]. Human ACE-2 is expressed in epithelial cells of the lung and serves as an entry receptor site for SARS-CoV-2 spike protein. ACE-2 genetic polymorphism (occurrence of different forms in the life cycle of an individual organism) represented by diverse genetic variants in the human genome has been shown to affect virus-binding activity suggesting a possible genetic predisposition to COVID-19 infection. Thus, analysis of genetic variants and genome sequencing from asymptomatic, mild or severe COVID-19 patients should be performed to classify and predict people based on their vulnerability or resistance to potential COVID-19 infection [24]. Genome sequencing is also critical in determining new variants of the virus among the infected population.

The entire genome of the 2019-novel coronavirus is more than 80% similar to the previous human SARS-like bat CoV [25]. Thus, previously used animal models for SARS-CoV can be utilized to study the infectious pathogenicity of SARS-CoV-2. CRISPR-mediated (see CRISPR, Chapter 6, page 168 and below) genetically modified hamsters or other small animals can be utilized for the study of the pathogenicity of novel coronaviruses.

Finally, an interesting finding was made among SARS-CoV-2-infected patients. Researchers found a haplotype (a group of genes inherited together from a single parent) on chromosome 12 that reduces the risk of severe Covid-19 infection. This genetic mutation is associated with about a 22% reduction in relative risk of becoming severely ill with COVID-19 when infected by SARS-CoV-2. This region encodes proteins that activate enzymes (proteases) that are important during infections with RNA viruses. The genetic region involved affects the body's immune response to RNA viruses such as the coronavirus. This is a mutation that has been passed down over the millennia because it is assumed to help people survive the frequent viral infections among humans [26]. It reminds me of the negative evolutionary correlate we spoke about back in Chapter 6 (page 168) regarding the "pro-cancer" programmed death protein on the T cell. That one was theorized as "culling the herd" while this one seems to promote phylogeny (evolutionary history of a species). Don't you wish "natural selection" and Darwinism would make up its mind?

4.6. Autoantibody rogue B-cell association with COVID-19 [27]

As mentioned in Chapter 5, late in the proofreading portion of this manuscript (late 2021), new findings were revealed regarding the association of memory B cells (MBCs), *aka* autoantibody rogue B-cells, with late COVID-19 infections. Researchers at Rockefeller University, Yale University and international research teams [28] detected these autoantibodies that could neutralize and lower, relevant concentrations of interferons. Their initial studies included 3595 patients with critical COVID-19 that were confirmed among individuals admitted to an intensive-care unit with advanced COVID-19 infections. Overall, 13.6% of these patients possessed autoantibodies, with the proportion ranging from 9.6% of those below the age of 40, up to 21% of those over 80.

This cohort study indicated that around 10% of people with severe COVID-19 had autoantibodies that attack and block type 1 interferons and their critical role in fighting off viral infections. Further studies on 35,000 blood samples of healthy in patients found an increase in B-cell autoantibodies against type 1 interferon ranged from 9.6% in patients below age 40 up to 21% in patients over 80. Autoantibodies were also present in 18% of people who had died of the disease. This massive increased prevalence in patients over 80 largely explains the high risk of severe COVID in people in the elderly population. These studies seem to indicate that rogue B-cell autoantibodies are a cause, rather than a consequence, of critical COVID-19.

5. Clinical considerations for coronavirus (SARS-CoV-2) infection

5.1. Clinical manifestations (signs and symptoms)

Reported illnesses with the novel coronavirus have ranged from mild symptoms to severe illness and death for confirmed COVID-19 cases. The symptoms may appear 2–14 days after exposure (based on the incubation period of SARS-CoV viruses). As with any infectious disease, the array of symptoms can vary considerably, but there are eight cardinal symptoms in adults and children (and other possibilities) which are the defining complex of the clinical disease [29], including:

In adults:	In children (age 5 to 17):	Other possible symptoms:	
1. **Loss of taste;**	1. Loss of taste	1. Severe fatigue;	9. Sore eyes;
2. **Loss of smell;**	2. Loss of smell;	2. Heavy arms/legs;	10. Sneezing;
3. **Fever;**	3. Fever;	3. Tightness in chest;	11. Diarrhea;
4. **New persistent cough;**	4. Headache;	4. Hoarse voice;	12. Sore throat;
5. **Shortness of breath;**	5. Shortness of breath;	5. Nasal congestion;	13. Difficult sleeping;
6. **Chills;**	6. Chills;	6. Dizziness;	14. Abdominal pain
7. **Loss of appetite;**	7. Loss of appetite;	7. Chest pain;	15. Numbness/ tingling
8. **Muscle aches.**	8. Muscle aches.	8. Nausea and vomiting	

Elderly and immune compromised patients are at greater risk for contracting the virus and for poor outcomes. However, significant numbers of young and healthy people are also being reported with severe infections, though generally with better outcomes. Spread occurs through respiratory droplets produced when an infected person coughs or sneezes. These droplets can land in the mouths or noses of people who are nearby or possibly be inhaled into the lungs [30].

Older age, obesity, and comorbidities have consistently been reported as the greatest risk factors for unfavorable prognosis or protracted disease, called “post-COVID syndrome,” “long COVID,” or “long haulers syndrome.” [31] This syndrome however, is found in a full range of COVID-19 patients, with symptomatology ranging from severe to nonexistent. The syndrome itself includes all sorts of problems with inflammatory responses in the brain (“brain-fog”), around the heart (myocarditis), around the nerves (neuropathies), around the muscles (myosititis), etc. It's clear that in addition to the immediate clinical effects of SARS-CoV-2, the novel coronavirus can have long-term manifestations, experts say [32]. Less clear so far has been how the number and types of comorbidities influence outcomes. An epidemiologic clarification was provided through a nationwide Chinese retrospective cohort study [33] involving 1590 PCR-confirmed (see Antigen testing below) COVID-19 cases (mean age, 49 years; 43% female) diagnosed between December 11,

2019, and January 31, 2020. The most common symptoms were fever, dry cough, and fatigue (88%, 70%, and 43%, respectively). In addition, there are reports of neurological symptoms, such as cognitive changes, or "brain fog" (suspected brain invasion of macrophages suppressing neural transmission—see also Chapter 4, page 82), headaches, paresthesia, and dysautonomia (a group of medical conditions caused by problems with the autonomic nervous system—ANS).

According to the 2019 American Thoracic Society/Infectious Disease Society of America guideline for community-acquired pneumonia criteria [34], 16% of the cases were considered severe. Reported proportions with comorbidities included 17% hypertension, 8% diabetes, 4% cardiovascular disease, 2% cerebrovascular disease, 2% chronic obstructive pulmonary disease, 1% chronic kidney disease, and 1% malignancy. At least one comorbidity was significantly more common in severe than in nonsevere cases (33% vs. 10%). Obesity puts those with COVID-19 at particularly high risk of death, more so than related risk factors such as diabetes or hypertension, according to a study of patient records by researchers from Kaiser Permanente [35]. In people with rare autoimmune diseases (RAIDs, some listed in Table 5.1, page 98), the risk of early death has risen with COVID-19. The most common RAIDs were giant-cell arteritis (22%), systemic lupus erythematosus (22%), juvenile inflammatory arthritis (13%), unspecified arteritis (12%), and polymyositis (10%).

5.2. Diagnostic testing [36]

The clarion call during the early stages of the COVID-19 pandemic was "Testing, Testing, Testing." Tracking ("contact tracing") an invisible virus is one of the most valuable ways to control it, and the most effective strategy to accomplish that goal starts with building a comprehensive system to test anyone who may be infected. Upon accomplishing that, those positive cases can be isolated and "contact traced" (identifying persons who may have come into contact with the infected person) and testing them as well and isolate all positive cases.

Other indirect biomarkers are being identified as diagnostic indicators for the degree and severity of a SARS-CoV-2 infection. In Chapter 1 (page 14), a malfunction of interferon (IFN-1) was identified as attributing to an increase of at least 3.5% of patients with life-threatening COVID-19 disease. Other studies of elevated concentrations of inflammatory cytokines and blood markers including C reactive protein, lactate dehydrogenase, and other digestive enzymes demonstrate the gut microbiome being linked with the severity of COVID-19. The gut microbiota dysbiosis after disease resolution can also contribute to persistent symptoms ("long COVID"), highlighting the diagnostic importance of gut microorganisms in inflammation and COVID-19 [37]

The definitive "diagnostic" process in diagnosing COVID-19 is conducted through two types of tests (below), one testing for the antigen (people who

are currently infected) and second testing for antibodies to the antigen (people previously infected who have developed antibodies to the virus). Regrettably, contact tracing has not proven valuable (I can attest to this personally having been a volunteer tracer) due to subjects reluctance to share necessary contact information.

5.2.1. Antigen testing

An antigen test reveals if a person is actively infected with the SARS-CoV-2 virus. The test detects certain proteins that are part of the virus. Using a nasal or throat swab to get a fluid sample, antigen tests can produce results in minutes. Because these tests are faster and less expensive than molecular tests (below), some experts consider antigen tests more practical to use for large numbers of people. Once the infection has gone, the antigen disappears. A positive antigen test result is considered very accurate, but there's an increased chance of false-negative results due to testing procedures, meaning it's possible to be infected with the virus but have negative antigen test results. Therefore, antigen tests aren't as sensitive as molecular tests (below). But antigen tests are readily available in that they already exist for strep throat, influenza, tuberculosis, HIV, and other infectious diseases.

Viral (antigen) tests identify the virus in samples from your respiratory system, such as a swab from the inside of your nose. It is possible to isolate the coronavirus from respiratory secretions, blood, urine, and fecal samples for diagnostic testing. Clinically, infections can be diagnosed with respiratory viral panels that are widely commercially available.

5.2.2. Molecular genetic test (PCR test)

This test detects genetic material of the virus using a lab technique called PCR. Also called a PCR test, a healthcare worker collects fluid from a nasal or throat swab or from saliva. Results may be available in minutes if analyzed onsite or 1–2 days if sent to an outside lab. Molecular tests are considered very accurate (kind of the gold standard) when properly performed by a healthcare professional, but the newer rapid tests appear to miss some cases. The FDA also approved certain COVID-19 at-home test kits, available only with doctor approval. It can be done with a nasal swab kit or a saliva kit. The sample is mailed to a lab for testing. The FDA warns consumers against buying unapproved home tests, because they may be inaccurate and unsafe.

5.2.3. Antibody testing

Antibody tests check a person's blood by looking for antibodies, that may (or may not) tell if the person had a past infection with the coronavirus. Antibodies are proteins that help fight off the infections and thus can provide immunity and protection against getting the infection again (see Chapter 2). Neutralizing antibodies are specific to an antigen (the virus) and thus provide protection only against the specific disease associated with the antigen (in the case of coronavirus as the antigen, the disease

being COVID-19). If the person is exposed to the antigen (coronavirus) again, the antibodies produce "memory" toward the disease (remember the B_M cells and anamnestic protection from back in Chapter 1?). However, there are increasing reports of reinfection with the novel coronavirus suggesting that some coronavirus antibodies may not be neutralizing.

Except in instances in which viral testing is delayed, antibody tests should not be used to diagnose a current COVID-19 infection. An antibody test may not show if you have a current COVID-19 infection because it can take 1–3 weeks after infection for your body to make antibodies. To see if you are currently infected, you need a viral (antigen) test.

5.2.4. Genome sequencing [38]

Genome sequencing is essentially determining the order of chemical "bases" of a DNA molecule (see Chapter 3, page 55). Sequencing efforts in the early stages of COVID-19 helped determine the structure of the virus, as well as its early mutations that increased transmissibility and produced a massive pandemic. Sequencing in late 2020 and the beginning of 2021 began identifying the more virulent and transmissible variants in the UK, South Africa, and finally the highly virulent delta variant in the U.S.

In the United States, sequencing was conducted in only 0.3% of tested samples ranking it 43rd (embarrassing) in the global genome sequencing database project. Genome sequencing is essential in identifying, dealing with and tracking the spread of the newly emerging and increasingly virulent and transmissible SARS-CoV-2 variants. Such transmissibility suggests that these variants are already widespread. The CDC announced doubling of the U.S. sequencing effort that is expected to find more variants in that the virus can mutate every time it transmits to a new host. With enough mutations, a strain may be able to evade current vaccines. If a vaccine-resistant strain is identified in the future, vaccine research will have to be directed through evidence-based data. That evidence will only come from genome sequencing. (You can tell that this prescient paragraph was written prior to the delta variant surge in 2021.)

5.3. Treatment and management strategies [39]

Care for coronavirus patients is supportive in nature and may include rest, supplemental oxygen, fluid administration, and, for critically ill patients, being managed in intensive care units and receiving rescue therapies such as extracorporeal membrane oxygenation (pulmonary ventilation). Stringent infection control is critical to preventing transmission to caretakers, healthcare workers, and other patients. Droplet precautions (e.g., personal protective equipment (PPE) including surgical or procedure masks, gown, gloves, and face shields) are indicated during the treatment of all coronavirus patients, and such protocols for droplet-spread respiratory viruses that are part of hospital infection control practices. Additional respiratory precautions may also be appropriate during aerosol-

generating procedures.

At the time of the writing of this Chapter on COVID-19, treatment and management strategies continue to grow, some proving effective and some ineffective. In that this is being written at the height of the pandemic (early 2021), it must be considered a prospective view of appropriate treatment and management as recommended by the medical experts guiding us through this difficult period. It will be of interest to the readers and future planners in the months and years ahead, to evaluate retrospectively which of these treatment and management approaches proved to be of most value. Hopefully, it will be an insightful lesson to future generations in their preparedness and response to epidemics and pandemics they may face. Future readers of this book will be able to retrospectively assess the strengths and weaknesses of each.

5.3.1. General measures

5.3.1.1. Basic preventive steps

(1) Shelter-in-place or "self-isolation" (remain in your home with only absolutely necessary outdoor activities);
(2) Social distancing (separation of >6 to 10 feet between people);
(3) Avoid gatherings of more than 5 to 10 people;
(4) Wash your hands copiously and frequently;
(5) Face masks (at first CDC and surgeon general suggest for use only if infected, now it's strongly recommended for fulltime use —N90 masks preferable);

(6) If symptoms occur (fever, cough, chills, aches, and pains), get tested and if positive, selfquarantine for minimum 14 days and retest ×2 before assuming normal activities;
(7) If symptoms advance over 2–3 days, seek medical attention.

5.3.1.2. Mitigation

This process includes procedures and policies to reduce risks of infectious spread. Results of mitigation are measured by "flattening the (modeling) curve." This is an inverted bell shape curve with the x-axis representing time and the y-axis representing number of cases [40]. Not pretty during surges!

5.3.1.3. Contact tracing

Epidemiologists, or "disease detectives," start with the index patient, sometimes called "patient zero." Depending on what they already know about that patient's condition—how the disease is spread, its natural history, what symptoms it causes—interview the patient to learn about their movements and identify all close contacts (persons, places, and things). Based on the answers, public health workers contact each associated person to explain their risk, offer screening for the infection and

conduct regular monitoring for symptoms of the infection. As mentioned above, this important public health measure is not progressing well due to limited “tracer personnel” and public resistance to sharing information.

5.3.1.4. Modeling

(1) Study the mechanisms by which disease is spreading (i.e., investigative epidemiologic and public health analysis);
(2) Monitor (graphically) through testing positive case volumes, death rates, and other vital statistics;

- Mortality;
- New cases (total and per 100,000 pop.);
- Hospital admissions;
- Intensive care admittance;
- extracorporeal membrane oxygenation (pulmonary ventilation)

(3) Predict the future course of an outbreak; and
(4) Evaluate strategies to control a pandemic. These strategies are developed through the modeling data described above.

5.3.2. Immunotherapeutics

It appears that SARS-CoV-2 infection has two phases. The early phase includes the infectious stage (approxiamtely 3 to 9 days) where the virus is replicating followed by the later stage (7 to 21 days) where the disease is driven by an exaggerated immune/inflammatory response to the virus. This is the phase that leads to tissue damage, organ failures and oftentimes, the post-COVID syndrome or long haulers syndrome. Based on this understanding, and as has been shown in clinical outcomes, antiviral therapies would have the greatest effect early in the course of time and unlikely to be more beneficial in the later stages of the disease.

(You might want to re-read the therapeutics and immunotherapies discussed in Chapters 5 and 6. Other than vaccines [which in essence are themselves immunotherapeutics], these immunomodulating drugs, particularly the monoclonal antibodies [see Chapter 5, Table 5.7] are proving to be [in conjunction with proper public health measures] a significant hope for the future.)

5.3.2.1. Monoclonal antibodies

From the previous chapters, I'm sure by now, you appreciate the significant benefits monoclonal antibodies (any drug with the name suffix, “… mab”) are providing to humanity (thanks to “our immune friend” and heroes like Dr. Fauci, Dr. Francis Collins [NIH Director] and others), so too are its benefits being recognized in COVID-19 therapy. As previously described, these are laboratory engineered antibodies used to mimic the immune system's own antibodies for a specific antigen (see Chapters 2 and

4).

In the early stages, usually when the patient is at home, monoclonal antibodies have proven effective in limiting the infectious stage. The most effective monoclonals (as of September 2021) have been Bamlanivimab and the combination of casirivimab plus imdevimab [41]. Based on clinical trials and their performance on early infections, the FDA issued EUAs in November 2020 [42] for use in treatment of outpatients with mild to moderate COVID-19 who are high risk for progressing to severe disease and/or hospitalization. Other monoclonal antibodies including interleukin-6 receptor antagonists (suppressing ILK-6), tocilizumab and sarilumab have also been shown to improve outcomes and survival rates, especially when used in combinations.

Regeneron, the combination of casirivimab and imdevimab (together called REGN-COV2), is directed against the spike protein of SARS-CoV-23 for use in patients with early infection. (As effective as they are, monoclonal antibodies should not be mistaken or substituted for vaccine properties which are preventative. Monoclonal antibodies are therapeutics and used asap upon infection.) An August 2021 clinical trial showed 70% improvement in outpatients who had presented within 7 days after the onset of symptoms and within 72h after a positive result on quantitative RT-PCR testing of nasopharyngeal swab samples. Key end points were achieved including a reduction from baseline viral load from day 1 through day 7 and reduction in percentage of patients who had at least one Covid-19–related medically attended visit through day 29. One state in the U.S. (Florida) recommends this monoclonal treatment (free) in favor of vaccination (at 95% effective). First off, it is being used broadly in place of vaccination which, as described above, is inappropriate use. Second, the cost of one Regeneron treatment (infusion plus facility costs) ranges anywhere from $1250 to $6500 versus $20 for one vaccination [43]. It's hard to believe that such a vaccine strategy alternative is not in the best interest of the public health. Unfortunately, sometimes politicians preempt science.

San Francisco-based Vir Biotechnology has identified several human neutralizing monoclonal antibody (mab) candidates against SARS-CoV-2. The antibody's ability to neutralize the SARS-CoV-2 live virus has been confirmed in two different laboratories. It binds to an epitope, the specific site on the viral antigen molecule that is also seen on the SARS-CoV-1 virus that causes SARS. This means the antigen is highly conserved and less likely to disappear should the viruses mutate or develop resistance to the antibody [44].

These results complement the findings of a trial that evaluated three doses (700mg, 2800mg, and 7000mg) of a single monoclonal antibody, bamlanivimab (LY-CoV555). Reductions in nasopharyngeal RNA levels of SARS-CoV-2 were detected after 3 days of treatment in all groups with a greater decline in the combined-dose bamlanivimab group than in the placebo group. The results suggest that monoclonal antibodies, when administered early in the infectious period serve as an effective antiviral

agent to reduce the viral load in the nasopharynx. The effects of monoclonal antibodies and other drugs on viral load may prove to be an important criterion for the development of agents to treat early Covid-19 [45].

5.3.2.2. Convalescent plasma (serum)

Plasma can be collected from the blood of patients who have recovered from COVID-19. The red and white blood cells are separated and put back into the donor's bloodstream while the blood plasma, rich with virus-fighting antibodies is kept aside. In one such experiment, 403 monoclonal antibodies were isolated from three convalescent COVID-19 patients. They showed that the patients had strong immune responses against the infecting viral protein, a complex that binds to receptors on the host cell. From this information, a subset of antibodies from the serum was able to neutralize the virus. Nonetheless, late 2020 results of convalescent plasma have proven equivocal [46].

5.3.2.3. Dexamethasone (and corticosteroids)

As discussed above and in detail in Chapter 4, chronic inflammatory organ diseases (e.g., heart, lungs, kidneys) may occur in severe Covid-19, with a subgroup of patients having markedly elevated levels of inflammatory biomarkers. Several therapeutic interventions have been proposed to mitigate inflammatory organ injury in viral pneumonia including glucocorticoids (i.e., dexamethasone). Glucocorticoids have been widely used in syndromes closely related to Covid-19, including SARS, MERS, severe influenza, and community-acquired pneumonia. However, the evidence to support or discourage the use of glucocorticoids under these conditions is inconclusive. In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support. Other steroids are also beginning to show some promising results during early stages of the disease.

A readily available, inexpensive corticosteroid, dexamethasone, has been found to improve survival in hospitalized patients who require supplemental oxygen, and its greatest effect observed in patients who require mechanical ventilation. Therefore, the use of dexamethasone is strongly recommended for seriously ill patients in the hospital setting but not advised for patients not on ventilation [47].

5.3.2.4. Antiviral drugs [48]

A universal vaccine effective against all viruses including SARS-CoV-2 is the holy grail of immunology and vaccinology. But short of that, current vaccines are not sufficient or even predictable in treating viruses, especially their mutations and variant infections of RNA viruses (like coronaviruses). Different from recombinant and mRNA vaccines that manipulate the body’s immune response to the virus and its genetics,

antiviral drugs attempt to boost the immune defense to inhibit viral development. They block receptors so viruses cannot bind to and enter healthy cells and they lower the amount of active virus in the body. Antivirals may be broad spectrum and treat a variety of viruses while others target a specific viral protein to disable the virus and remain nontoxic to the host cells. Thus, most antivirals are considered relatively harmless to the host, and thus can be used aggressively (large dosages) to treat infections (e.g., acyclovir) [51].

Among the growing list of antiviral drugs for COVID-19, Molnupiravir by Merck/Ridgeback Biotherapeutics and Paxlovid by Pfizer (see below) have proven effective in certain forms and variants of the SARS-CoV-2 virus and have been given FDA emergency use authorization approved. Other drugs, FDA approved for uses other than antiviral therapy, are being promoted as having antiviral qualities based on anecdotal evidence. Scientific-based studies have proven these drugs to be questionable or wholy ineffective in the treatment of coronaviruses and have even shown adverse effects in their use for such therapy (see below). These drugs include (but are not limited to) hydroxychloroquine (combined with the antibiotic Azithromycin) and Ivermectin (an antiparasitic drug use mostly in veterinary medicine).

5.3.2.4.1. Paxlovid (Pfizer)

Paxlovid (nirmatrelvir/ritonavir) is a protease inhibitor, similar to those used against HIV. SARS-CoV-2 uses its cellular enzymes (protease) to replicate its RNA-containing "polyproteins" (see Life Cycle, page 189). By blocking the enzyme's activity, the drug prevents the production of new, functional viral particles. Paxlovid is quickly broken down in the body, so it needs a booster in the form of a second drug called ritonavir (also a protease inhibitor) to keep it active for a longer period in the host. Notwithstanding potential drug–drug interactions, these drugs have shown significant promise with a 90% reduction in hospitalization rates [49].

5.3.2.4.2. Molnupiravir (Merck/Ridgeback Biotherapeutics)

Molnupiravir is known as a nucleoside analogue. It mimics one of the RNA proteins that make up SARS-CoV-2. Once inside cells, the virus uses a polymerase enzyme to attach to its RNA and assemble them into new copies of viral RNA. The virus needs a template for construction of new viral RNA and molnupiravir interrupts this template and causes the virus to continuously mutate until it virtually destroys itself with defective genetic material. Due to some side effects from the drug, it is used only in high-risk patients with advanced disease [50].

5.3.2.4.3. Remdesivir

This antiviral drug is thought to interfere with the mechanism that coronavirus uses to make copies of itself (see Fig. 7.1 and discussion on Life Cycle above). Scientists are still working out exactly how that occurs.

A preliminary report published in The New England Journal of Medicine showed that the drug shortened recovery time for people with COVID-19 from an average of 15 days to about 11 days. The drug also seems to show increased benefits when used in combination therapies (e.g., with Baricitinib and monoclonal antibodies).

In the advanced stages of COVID-19, Remdesivir is the only FDA approved drug. It is recommended for use in hospitalized patients who require supplemental oxygen. However, it is not routinely recommended for patients who require mechanical ventilation because of a lack of data showing any benefit at this advanced stage of the disease. The addition of Baricitinib with remdesivir (i.e., a combination) proved to be superior to Remdesivir alone in reducing recovery time and accelerating improvement in clinical status among hospitalized Covid-19 patients [51].

5.3.2.4.4. Hydroxychloroquine (Plaquenil) combined with azithromycin (Zithromax)

A small sample survey showed that hydroxychloroquine treatment (a biologic used for malaria and lupus) is associated with viral load reduction in COVID-19 patients and its effect is reinforced by azithromycin (an antibiotic). A study reported in the New England Journal of Medicine concludes that results do not support the use of hydroxychloroquine at present, outside randomized clinical trials testing its efficacy. Further work is warranted to determine if these compounds could be useful as chemoprophylaxis to prevent the transmission of the virus without significant adverse effects. Continuing studies are proving increasingly negative and demonstrating more potential adverse effects than benefits. These clinical findings were never considered when hydroxychloroquine was enthusiastically promoted by a U.S. political figure (a president to be exact) with no medical knowledge [52].

5.3.2.4.5. Ivermectin

This drug is approved by the FDA to treat people with intestinal strongyloidiasis and onchocerciasis, two conditions caused by parasitic worms. In addition, some topical forms of ivermectin are approved to treat external parasites like head lice and for skin conditions such as rosacea. Some forms of animal ivermectin are approved to prevent heartworm disease and treat certain internal and external parasites. It is important to note that these products are different from the ones for people, and safe only when used in animals as prescribed. Currently available data do not show ivermectin is effective against COVID-19 [53].

5.3.2.4.6. Other developing antiviral drugs for COVID-19

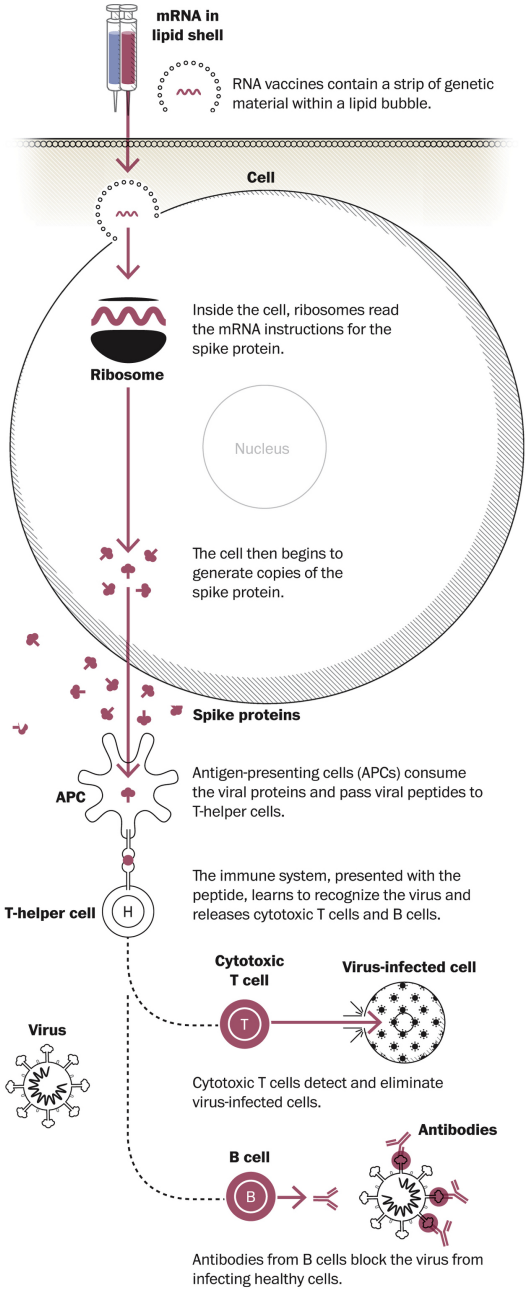
Besides continuing development of new vaccines to address SARS-CoV2 resistant variants, new antiviral drugs will continue to be developed as adjunctive therapies to vaccines and any other evolving immunotherapeutic measures to COVID-19. No doubt by the time you are reading this, beyond all of the drugs and treatment modalities listed below

and mentioned in this section, there will be an array of new therapeutic measures being implemented for patient treatments and hopefully, for prevention [54].

- Interferons: antiviral cytokines under investigation;
- Lopinavir/Ritonavir and other HIV protease inhibitors
- Nitazoxanide: antiparasitic drug under investigation
- Lopinavir/Ritonavir and other HIV protease inhibitors
- Fluvoxamine: an antidepressant pill as an antiinflammatory
- Budesonide: an inhaled steroid used to prevent asthma symptoms

5.3.3. Vaccines [55]

By definition, a vaccine is a biological preparation that provides active, innate, and adaptive immunity to a particular infectious disease (e.g., measles, flu, SARS-CoV-2) by stimulating antibodies or manipulating messenger RNA (mRNA) to attack the source of the infection. The traditional approach has been to develop an agent that resembles the disease-causing microorganism made from weakened or killed (called an attenuated form or viral vector) fragments of the offending microbe, its toxins, or one of its surface proteins. This process induces a subclinical antigen stimulus that is recognized by the immune system that produces corresponding immune cells and antibodies, but without inducing clinical disease. In the novel coronavirus, the spike protein was targeted for most of the vaccine human clinical trials. Research centered on how the immune system, particularly B and T cells, responded to the spike protein and revealed the classic B cell response of producing the antibodies that recognize SARS-CoV-2, while T cells play their classic role in supporting the development of the B-cell response.



Sources: National Institutes of Health; Centers for Disease Control and Prevention; Nature Research; Columbia University

Figure 7.2 mRNA (messenger RNA) vaccine.An mRNA molecule imbibed with an engineered strip of genetic material to mimic the RNA of the virus. It is injected into the patient and generates copies of the spike protein which produce APCs that produce an

antibody immune response that destroys the virus. Washington Post. 2020.

Vaccine research teams also work on the development of vaccines using the virus itself, in a weakened or inactivated form while some use viral-vectors wherein a virus such as measles or adenovirus (recombinant serotype Ad5) is genetically engineered so that it can produce or "mimic" corresponding proteins to the target microbe. The teams that showed the greatest success (as of early 2021) against the RNA novel coronavirus used genetic instructions in the form of messenger RNA (mRNA) to prompt a subclinical immune response from the virus.

5.3.3.1. mRNA vaccines [56]

The science of the mRNA vaccine is an elegant model of immunology and genetics technology (Fig. 7.2). An RNA virus (e.g., novel coronavirus) means its genetic material is encoded in RNA rather than DNA. Once the virus is inside our cells, it releases its RNA and makes long viral proteins to compromise the immune system (see page 190 and Fig. 7.1). Inside the cells, the cell ribosomes read the mRNA instructions for the spike protein and the cell begins to generate copies of it. Genomic transcription and translation (see Chapter 3, Genetics and Genomics, page 45) produce copies of the virus' surface receptors (spike proteins, in the case of novel coronavirus). Then, as the patient's immune system recognizes a "foreign invader," it initiates an APC/ T_H and T_C response (remember those from Chapter 1?) that release T_H cells that generate cytotoxic T_C and B cells (if you'd like, go back to Chapter 1, Fig. 1.3 and 1.4 to review this innate immune process). The T_C cells go to work doing their job of phagocytizing the virus while the B cells generate antibodies that bind and block the virus from infecting healthy cells [57]. Goodbye virus…at least for 6 to 12 months they are projecting at which time we will probably be looking at COVID-19 booster shots.

One of the weapons in our cells is an RNA surveillance mechanism called nonsense-mediated mRNA decay (NMD) that protects us from many genetic mutations that could cause disease. The genome of COVID-19 is a positive-sense, single-stranded RNA that can evade NMD and prevent it from degrading RNA by producing proteins that interacts with certain proteins that modify the chemical structure of RNA. With the progression of new viral strains, the mRNA vaccines can be easily genetically reprogrammed to recognize mutant viral strains (called variants) and allow for the rapid development (within weeks) of second-generation vaccines that directly target processes critical to a virus's life cycle [57].

The first vaccines approved by the FDA in early 2021 were the mRNA (messenger RNA) technology that had been in development for a number of years but not yet used or approved. Two pharmaceutical manufacturers, Pfizer and Moderna, were the first to produce a viable product for delivery, distribution, and storage. All three of those aspects of successful production proved as challenging as the science itself. Storage was the major issue in that Pfizer's product needed storage at -94°F and Moderna

-50°F. Since initial distribution, those temperatures were moderated (decreased) after extended testing. But the logistics of distribution and delivering sufficient drug and associated requirements (syringes, needles, and trained vaccinators) in most countries proved problematic, especially given the need for two shots given 3 weeks apart.

Subsequent vaccines (mRNA and viral vector technologies) requiring normal storage temperatures and only one shot have been subsequently (as of this writing date) approved and introduced. Success in this type of mRNA vaccine proved 95% effective in December 2020 and led to worldwide use of Pfizer's BNT162b2 and Moderna's ChAdOx1 mRNA vaccines since 2021. This form of mRNA vaccine has also proven effective against variants of the novel coronavirus [59].

AI and immunoinformatics (see below) play a central role in vaccines by suggesting components understanding viral protein structures, and helping medical researchers hunt through tens of thousands of relevant research papers at an unprecedented pace. AI supported preclinical studies in mice of a candidate vaccine based on this spike protein are already underway at NIH's Vaccine Research Center (VRC) [58]. But there will be many more steps after that to test safety and efficacy, and then to scale up to produce millions of doses. National Institute of Allergy and Infectious Diseases is working with numerous biotechnology companies (AstraZeneca, Pfizer, J&J, Moderna, et al.) to use the latest findings developed in vaccine research using messenger RNA (mRNA), molecules that serve as templates for making proteins. The goal is to direct the body to produce a spike protein in such a way to elicit an immune response and the production of antibodies. Other forms of vaccine candidates are also in preclinical development.

5.3.3.2. CRISPR-Cas13 and RNA screening [60]

A new Cas13 RNA screen (vs. Cas 9 from Chapter 6, page 168) has been developed to establish guide RNAs for the COVID-19 coronavirus and human RNA segments that could be used in vaccines, therapeutics, and diagnostics. Similar to CRISPR-Cas9 (see Chapter 6, page 168), a novel Cas13-based editing tool enables researchers to target mRNA (vs. DNA for the Cas9 enzyme) and knockout genes without altering the genome. Using the CRISPR-Cas13 enzyme, researchers have created a genetic screen for RNA, currently designed for use on humans, that they say could also be used on RNA containing viruses and bacteria.

The developers have used their parallel-screening technique to create optimal guide RNAs for the SARS-CoV-2 coronavirus that could be used for future detection and therapeutic applications. The platform is optimized to run massively parallel genetic screens at the RNA level in human cells because it is based on the CRISPR-Cas13 enzyme that targets RNA instead of DNA. The data are collected by targeting thousands of different sites in human RNA transcripts to create a predictive model to expedite identification of the most effective Cas13 guide RNAs.

5.3.4. Vaccination (immunization)

Vaccination is the act of getting a vaccine, usually in the form of an injection into the arm of a person (immunization) to protect against a disease. Testing for an effective vaccine begins with giving the vaccine to animals such as mice or monkeys to see if it produces an immune response. Then Phase 1 vaccinates a small number of people to test safety and dosage as well as to confirm that it stimulates the immune system. Phase 2 includes hundreds of people split into groups (viral injected and placebo, called a double-blind study where members of the two groups are kept unknown, "blind" to the researchers), such as children and the elderly, to see if the vaccine acts differently in them as well as safety and ability to stimulate the immune system. Phase 3 injects the vaccine into thousands of people (again, two groups) to see how many become infected, compared with volunteers who received a placebo. These trials can determine any rare side effects that might be missed in earlier studies.

Finally, if the vaccine protects against the coronavirus in at least 50% of vaccinated people it is considered effective and regulators decide whether to approve the vaccine or not. During a pandemic (or any such studies), a vaccine trial may be terminated if the test group is demonstrating too negative a result. Conversely, if the test results are proving highly effective (much better result in the test group that the placebo group), the FDA may issue an EUA (emergency utilization authorization) even before getting formal approval. The mRNA vaccines (Pfizer and Moderna) proved highly effective at 95% and 94%, respectively, and received immediate EUA in January 2021 [61].

At least seven teams are developing vaccines using the virus itself (J&J just got EUA for a viral vector vaccine with 75% effectivity and AstraZeneca received UK approval), in a weakened or inactivated form. Around 25 groups say they are working on viral-vector vaccines. A virus such as measles or adenovirus (recombinant serotype Ad5) is genetically engineered so that it can produce coronavirus proteins in the body. At least 20 teams are aiming to use genetic instructions (in the form of DNA or RNA) for a coronavirus protein that prompts an immune response. Many researchers are now experimenting with injecting coronavirus proteins directly into the body to mimic the coronavirus's outer coat. When you read this Chapter, it's most likely you will know.

5.3.4.1. R naught (R^O or R0) and herd immunity

The concept of herd immunity is an epidemiological formula in which a sufficient amount of people are immunized or vaccinated against a pathogen, thus reducing the rate of infection throughout the population. The vaccination levels must produce a threshold called the "R-Naught" or R_O (The SIR ["susceptible-infectious-recovered"]) formulation, a factor that determines the transmissibility of the pathogen. It denotes the average number of secondary cases of an infectious disease that 1 case would generate in a completely susceptible population. That is, when one

infected person infects greater than one other person, a potential exponential increase in infections results leading to an epidemic or pandemic. If, however, transmission on average remains below an R_O of one person, this will result in a decreasing spread in infection and eventually into a majority of the population (an estimated 70%–80% needed) to produce "herd immunity."

In the absence of a vaccine, developing herd immunity to an infectious agent requires large amounts of people actually being infected, developing antibodies to the infectious agent and thus becoming immunized against future infection. Scientists are not always certain if this immunity is permanent or for how long it might last. But even assuming that immunity is long-lasting, a very large number of people must be infected to reach the 70%–80% herd immunity threshold required. During this process, mortality of certain infections like SARS-CoV-2 could reach unacceptable levels as occurred in Sweden where herd immunity was aspired to prematurely [62].

Nor does a pathogen magically disappear when the herd immunity threshold is reached. Rather, it only means that transmission begins to slow down and that a new epidemic is unlikely to start up again. An uncontrolled pandemic could continue for months after herd immunity is reached, potentially infecting many more millions in the process. These additional infections are what epidemiologists refer to as "overshoot." [63].

5.3.4.2. Human vaccines project

Researchers are comprehensively genetically sequencing the human immune (the "immunome") system, a system billions of times larger than the human genome. The goal is to encode the genes (the antibody-encoding genes—see Chapter 1, page 16) responsible for circulating B cell receptors. This can provide potentially new antibody targets for vaccines and therapeutics that work across populations. The Human Vaccines Project seeks to define the genetic predisposition of people's ability to respond and adapt to an immense range of diseases [64].

The SARS-CoV-2 COVID-19 pandemic will certainly expedite further progress on this critical area of clinical research. The study specifically looks at one part of the adaptive immune system, the circulating B-cell receptors that are responsible for the production of antibodies, considered the primary determinant of immunity in people. The receptors form unique sequences of nucleotides (DNA base compounds) known as receptor "clonotypes." [65] This creates a small number of genes that can lead to an incredible diversity of receptors, allowing the immune system to recognize almost any new pathogen (a little complicated, but give it a reread and you'll see what a great potential it has).

This Project marks a crucial step toward understanding how the human immune system works, setting the stage for developing next-generation health products, drugs, and vaccines through the convergence of genomics and immune monitoring technologies with machine learning and artificial

intelligence (AI) [66].

5.3.4.3. A vaccine epitaph [67]

Finally, a sad chapter in the U.S. history of vaccinations lingers in the minds and hearts of people of color. It has generated a mistrust of the medical system among some Black Americans regarding vaccination and it produced a stark disparity in morbidity and mortality for those who got COVID-19 vaccinations early in the U.S. As of February 2021, more than 60% of Caucasian American were vaccinated versus roughly 6% of African Americans. This mistrust is rooted in the infamous study of a vaccine for syphilis that left Black men in Tuskegee, Ala., to suffer from the disease. In 1932, the U.S. Public Health Service recruited hundreds of Black men as human subjects for the study (399 men with syphilis and 201 without).

The researchers offered free meals and checkups, but never explained that participants would be human subjects in a study designed to withhold medical treatment. “I think a part of the challenge is that there's still considerable anxiety about the vaccine,” says Amir Farooqi, director of the Central Alabama VA. Dr. Reuben Warren, director of Tuskegee University's bioethics center, notes the mistrust of the healthcare system among African Americans is “both historical and current.”

6. Immunoinformatics (computational immunology) [68]

The explosion of new immunological data through increased research in understanding the immune system, particularly in infectious disease pathogenesis and the application of the knowledge from bioinformatics, has led to a better understanding of the importance of the immune system through immunoinformatics (computational immunology). Through increased knowledge of the immune system, AI research, and the cost-effective, specific, and effective approaches like *in silico* immunoinformatics (scientific experimentation and research conducted or produced by means of computer modeling or computer simulation), the concerns for emerging and potentially resurging diseases caused by pathogenic organisms, antigenic variability/complex lifecycle of pathogens (see Fig. 7.1, life cycle, above) and the need of personalized vaccination can be combated on a molecular level. (Wow! That may have been the longest sentence in this entire manuscript. Maybe the copyeditors will rework it, cause I sure ain't going to try.)

AI and immunoinformatics are being used to better understand the structure of proteins involved in SARS-Cov-2 infection in search for potential treatments and vaccines (perfect example, the mRNA vaccine). Proteins have a three-dimensional structure, that is determined by their genetically encoded amino acid sequence (Next-gen sequencing [NGS] of genetic code), and this structure influences the role and function of the protein. An AI Google DeepMind system called AlphaFold [69] uses amino

acid sequencing and protein structure to make predictions to construct a “potential of mean force” that can be used to characterize the protein's shape. This system has been applied to predict the structures of six proteins related to SARS-CoV-2.

In silico immunoinformatics depends on experimental science (“wet lab”) to produce raw data for analysis. Thus, its predictions are not formal proofs of any concepts. They do not replace the traditional experimental research methods of actually testing hypotheses. The quality of immunoinformatics predictions depends on the quality of data and the sophistication of the algorithms being used (remember the good old, "garbage in – garbage out" axiom?). Sequence data from high-throughput analysis often contain errors. If the sequences are wrong, or annotations incorrectly, the results from the downstream analysis could be misleading as well (ergo, “garbage in—garbage out”). The future of immunological research will be enhanced by the ability to make discoveries in biologics (e.g., vaccines) more effectively and efficiently through combined AI and *in silico* immunoinformatics with traditional experimental research methods. Notwithstanding the credit certain narcissistic politicians like to take for the rapid development of COVID-19 vaccines, it was the combination of brilliant researchers, AI, and immunoinformatics that brought home the bacon in a desperate COVID-19 human crisis.

7. Epidemiology and public health considerations in COVID-19

7.1. Current epidemiologic considerations

The world celebrated the newly discovered vaccines in early 2021 that began the mitigation and reversal of the COVID-19 pandemic. The suffering and ill-effects of the novel coronavirus have been devastating to the world through its toll on lives and its ever-increasing death toll, not to mention the crippling economic effects it has had on individuals and governments.

Without a doubt the first hooray must go to the teams of research scientists at companies like Pfizer, Moderna, AstraZeneca, J&J, and others in varying stages of vaccine research. The second cheer should go to the governments of most industrialized countries who prioritized vaccine development with little concerns for costs of such initiatives. Certainly, included in that cheer must be the U.S.'s Operation Warp Speed that committed its best and brightest to answer the clarion call. Whereas, such successes in vaccine development had been experienced historically, none was accomplished in months of the initial and growing spread of the infectious disease. Rather, the world had to wait years, sometimes decades, and sometimes “never.”

The very existence of a fertile and brilliant body of worldwide researchers has been applauded for years by an appreciative public who have benefitted from their efforts. Also, accolades must be given to the

governments who offered selfless, humanitarian support in the form of leadership, some humble and some perhaps, ego-driven. But perhaps the greatest cheer should go to the contribution made by the immunology, genetic, and AI technologies that provided the research scientists and the tools needed to accomplish the task in record time. Those achievements by the research and scientific community started many years ago with the early work of heroes in immunology and genetic research mentioned throughout this book.

Answers are available to the researchers today within minutes to seconds, thanks to new methods of rapid whole genome sequencing (WGS) [70] and AI big data analytics. Indeed, the scientific work over the past 10–20 years, plus their concentrated efforts over just 6 months are truly the backbone of the success witnessed in the development of the COVID-19 vaccines. We must all be thankful for these accomplishments that have begun to reduce the human suffering and economic devastation brought upon the world from this COVID-19 pandemic. But we must also remain scrupulously vigilant.

Today, the impact of COVID-19 and its rapidly evolving variants portend equal or more disastrous effects than the Spanish Flu of 1918–19, the Asian Flu of 1957–58, the Hong Kong Flu of 2003, and the SARS (SARS-CoV-1 coronavirus) of 2003. SARS-CoV-2 novel coronavirus is a far more contagious member of the coronaviruses (CoVs), the large family of enveloped, positive-strand RNA viruses responsible for a substantial portion of upper respiratory tract infections. Many countries (e.g., China, Singapore, Hong Kong, South Korea, Italy, Spain, and the USA) have relied on an extrapolation of classic infection-control and public-health measures similar to those used for SARS-CoV-1 to contain the COVID-19 pandemic. They range from extreme quarantine measures, “shelter-in-place,” “social distancing,” to painstaking detailed contact tracing with hundreds of contact tracers. However, these measures may not be effective in the coming years for tackling the scale of COVID-19.

Vertically integrated digital and AI technologies are being introduced for monitoring, surveillance, detection, prevention of COVID-19, and to mitigate its spread and its direct and indirect impact to worldwide healthcare systems. The initial reaction in many countries to COVID-19 is for healthcare facilities to reduce or even cease many clinical services, including closure of clinics and postponement of medical appointments or elective surgeries. However, such strategies cannot be sustained indefinitely if the COVID-19 pandemic extends beyond 6 months. Healthcare systems should plan to use digital technology “virtual clinics” using telehealth consultations with imaging data uploaded from peripheral sites and interpreted remotely. This would ensure that patients continue to receive standard clinical care while reducing physical crowding of patients into hospitals. Chatbots staffed by health professionals can also provide early diagnoses as well as patient education. And blockchain technologies can coordinate hospital, clinics, and pharmacy patient information.

7.2. Public health considerations and recommendations

Undoubtedly, by the time you read this book, the public health literature and more so, programs and research in the epidemiology, bioscience considerations, clinical aspects, and immunological considerations regarding COVID-19 will have proliferated into a major body of new science and "disruptive technologies." Indeed, the reemergence of yet another more virulent SARS-CoV virus and global pandemic will emphasize the ongoing and permanent challenge that infectious diseases pose and the need for global cooperation and preparedness, even during "interim" periods.

A well-done opinion piece written by Michael Gerson in the Washington Post in late February 2021 entitled "Six takeaways from covid-19 that could shape our future," highlights the best public health advise we can "takeaway" from the COVID-19 pandemic [76]

1. We are in a brutal evolutionary struggle between humans and microbial pathogens. The pathogens evolve much faster than we adapt. A new pathogen emerges, on average, every 4–5 years. Covid-19 has been bad, but the larger danger comes from a novel influenza that has a high fatality rate and is highly transmissible before the development of symptoms. There is a 1% yearly probability of an influenza pandemic that could cause six million deaths or more.
2. About 75% of new emerging diseases are zoonotic (originating in animals). Humans amplify that threat in a variety of ways. Our appetites are insatiable for animal protein (e.g., pigs, cows, and god forbid, wet-markets). Deforestation is bringing humans into more frequent contact with wildlife such as bats (spreading infection). It has been well documented now that popular house pets (dogs and cats) can contract and transmit the coronavirus. Scientists in the Predict program have discovered 1200 animal-borne diseases over the past several years and estimate there may be 700,000 more we don't know about.
3. The world is "a little blue marble" and spreading disease to and from our borders in places such as Brazil, South Africa, or Britain can, as we are seeing with the coronavirus, lead to genetic variants that evade immunity, vaccine, and become potentially deadly. Fighting diseases in one country is not as effective as them being fought "everywhere."
4. The U.S. government failed to provide early and adequate support for testing and contact tracing with SARS-CoV-2. It failed in a timely manner to effectively distribute medical supplies and equipment, standardize epidemic data, and enforce rational triggers for stay-at-home orders and school closings. Such errors resulted in an inadequate response to the COVID-19

pandemic (and unspeakable death). We cannot allow such errors in adherence and commitment to public health guidelines to occur again.

5. A large number (perhaps a majority) of Americans failed to take relatively minor preventive steps such as mask-wearing and social distancing. Part of this was because of a president who consistently played down and politicized the public health crisis. But the problem runs deeper than political ineptitude and resistance to commonsense measures. Epidemiology and public health dictate the necessity of demographic assessments of age, comorbidity, socioeconomic factors, and basic living conditions in a pandemic or for that matter, any health-related issues. How would the U.S. have behaviored if political and societal actions had been more closely aligned and sensitive to these epidemiologic factors and risk of death? It requires conscientious, organized, astute, and empathetic governing to assess specific and generic risks to protect humanity.
6. Finally, calibrating our responses and responsibilities to the urgencies and dangers we face as a society, will protect the public health and improve the well-being of humankind in general. Attention to climate change, pollution, farming, deforestation, wildlife, health, precision health, disease prevention, and providing adequate federal planning, resources, and funding for the next pandemic is our only hope for a better future.

And I'll add one more to this list of takeaways regarding lessons learned from the COVID-19 pandemic regarding our personal health and wellness. A conscious effort toward physical activity and weight management in our lifestyle will bolster host antiviral, immune defense, and improve the vaccine immune response. I have tried to accentuate the importance and value of weight control numerous times throughout this book, but I failed to mention the importance of physical activity as well. A 30- to 60-min regimen of walking, running, gym workouts, or other physical sports can stimulate the ongoing exchange of important types of white blood cells between the circulation and tissues. Exercise-induced increases in antipathogenic leukocytes may also enhance immunosurveillance, reduce illness risk, and lower systemic inflammation. This pandemic should be a wake-up call to everyone that good health habits, health prevention, proper diet, and exercise are what we need to win this war.

I began this Chapter by reporting on the number of worldwide COVID-19 recorded cases and deaths to date. The number reminds me of a sad saying. “One death is a tragedy—2.5 million is a statistic.” We cannot let ourselves become inured to this sad calamity. Maybe if we think of it as 2.5 million personal tragedies (and growing), we'll realize what the world and each of us as caring individuals have endured through this apocalyptic pandemic. Will things get better? Certainly, the development of vaccines

and a path toward herd immunity is now our hope. But will we continue to face human tragedies, not statistics, of epic proportions in the future? As I stated at the beginning of this chapter, it is estimated that there are 380 trillion (10^{38}) viruses residing in environmental ecosystems throughout the world. Let us all hope and pray that the applications of immunology, genetic science, AI technologies, and mostly our personal and societal efforts will meet and defeat this public health challenge of infectious disease pandemics and will help humanity create a better place in which we and future generations all can live.

8. Brief research summaries on infectious diseases and COVID-19

(Reference citations for each research study presented below can be found in the corresponding footnote. Also, a listing of available scientific reference sources and databases used by the author are included in the book's Acknowledgments.)

By now, you have probably recognized my strong interest in AI, as I admitted to back in the Preface of the book. As I mentioned, I thought that the majority of readers of this will have some interest in the AI research directly related to the topics we've been discussing. AI research tends to be more practical in its applications than pure bioscience, laboratory research and thus, may be of more interest to readers of this book. I hope you have found some, if not all of the summaries of interest.

1. Forbes Magazine reported on a global AI database company, BlueDot, using an AI-powered algorithm, machine learning, and natural-language processing (NLP) to analyze information from a multitude of sources that can track over a 100 infectious diseases [72].

2. AI is playing an important role in evaluating the pathogenesis, diagnosis, and treatment of the SARS-CoV-2 virus. There is an urgent need to develop a system with AI-based machine learning capacity to analyze and integrate imaging-based, patient-based, clinician-based, and molecular measurements-based data, to fight the outbreak of COVID-19 and enable more efficient responses to unknown infections in the future [73].
3. Vaxign is a reverse vaccinology tool being used with Vaxign-ML machine learning tool to predict COVID-19 vaccine candidates. A study applied the state-of-the-art Vaxign reserve vaccinology and Vaxign-ML machine learning strategies to the entire SARS-CoV-2 proteomes including both structural and nonstructural proteins for vaccine candidate prediction. The results indicate for the first time that many nonstructural proteins could be used as potential vaccine candidates [74].

4. AI technologies are powerful tools against COVID-19 and widely used in combating this pandemic. A survey investigated the main scope and contributions of AI in combating COVID-19 from the aspects of disease detection and diagnosis, virology and pathogenesis, drug and vaccine development, and epidemic and transmission prediction. AI mainly focuses on medical image inspection, genomics, drug development, and transmission prediction, and thus still has great potential in this field [75].
5. On March 16, 2020, the White House issued a call to action for global AI researchers to develop new algorithms and data mining techniques to assist in COVID-19-related research. Within a short period of time, advanced machine learning techniques were developed and implemented to better understand the pattern of viral spread, further improve diagnostic speed and accuracy, develop novel effective therapeutic approaches, and potentially identify the most susceptible people based on personalized genetic and physiological characteristics. This is only the beginning of a permanent role AI will play in global healthcare [76].
6. One of the main challenges in medical microbiology is to develop novel experimental approaches that enable a better understanding of bacterial infections and antimicrobial resistance (especially in light of the COVID-19 pandemic). Today, the use of *in silico* experiments (research conducted by means of computer modeling or computer simulation) jointly with computational and machine learning offer an in depth understanding of systems biology, allowing us to use this knowledge for the prevention, prediction, and control of infectious disease. An in-depth knowledge of host–pathogen–protein interactions, combined with a better understanding of a host's immune response and bacterial fitness, is key determinants for halting infectious diseases and antimicrobial resistance dissemination [77].
7. IoTs (Internet of Things) are providing a platform that allows public-health agencies access to data for monitoring the COVID-19 pandemic. For example, the “Worldometer” provides a real-time update on the actual number of people known to have COVID-19 worldwide, including daily new cases of the disease, disease distribution by countries and severity of disease (recovered, critical condition or death). Johns Hopkins University's Center for Systems Science and Engineering has also developed a real-time tracking map for following cases of COVID-19 across the world, using the data collected from US CDC, the World Health Organization (WHO), the European Center for Disease Prevention and Control, the Chinese Center for Disease Control and Prevention (China CDC), and the Chinese website DXY [78].

8. Big data are providing opportunities for performing modeling studies of viral activity and for guiding individual country healthcare policymakers to enhance preparation for the outbreak. Using three global databases, WHO International Health Regulations, the State Parties Self-Assessment Annual Reporting Tool, Joint External Evaluation reports and the Infectious Disease Vulnerability Index, health authorities are performing AI modeling studies of “nowcasting” and forecasting COVID-19 disease activity throughout the world for public-health planning and control worldwide [79].
9. When the Covid-19 pandemic enters dangerous new phases, the critical question becomes whether and when to take aggressive public health interventions to slow down the spread of COVID-19. A study was undertaken to develop AI inspired methods for real-time forecasting and evaluating intervention strategies to curb worldwide spread. A modified autoencoder for modeling the transmission dynamics of the epidemics is being developed and applied to the surveillance data of cumulative and new Covid-19 cases and deaths from WHO, as of March 16, 2020. Total peak number of cumulative cases and new cases in the world with later intervention could reach 255,392,154 by January 2021. However, the total peak number of cumulative cases in the world with one-week earlier intervention were reduced to 1,530,276. We observed that delaying intervention for 1 month caused the maximum number of cumulative cases to increase 166.89 times, and the number of deaths increase from 53,560 to 8,938,725. Disastrous consequences if immediate action to intervene are not taken [80].
10. MIT published a paper describing the needed changes in three areas if we want AI to be useful in future pandemics. First, prediction through database companies using a range of NLP algorithms to monitor news outlets and official health-care reports in different languages around the world; second, machine-learning models with large datasets for examining medical images to catch early signs of disease that human doctors miss, from eye disease to heart conditions to cancer; third, identifying cures through big data analysis of drug trials and design algorithms to highlight biological and molecular structures matching drugs with candidates [81].
11. Advanced deep learning-based algorithms known as the convolutional neural network (CNN) exert a great effect on extracting highly essential features, mostly in terms of medical images. This technique using CT and X-ray image scans has been adopted in most of the recently published articles on the coronavirus with remarkable results. Furthermore, according to this paper, it can be noted and said that deep learning technology has potential clinical applications [82].

12. A new framework has been proposed to detect COVID-19 using built-in smartphone sensors (IoTs). The proposal provides a low-cost solution that ordinary people can use on their smartphones for the virus detection purposes. The designed AI enabled framework reads the smartphone sensors signal measurements to predict the grade of severity of the pneumonia as well as predicting the result of the disease [83].
13. AI and deep learning algorithms are being developed to enhance the detection and diagnosis of COVID-19. The need to provide access to accurate and low-cost tests for the diagnosis of COVID-19 is critical. Such AI algorithms can be used as an initial screening tool for suspected cases so that patients at higher risk could have confirmatory laboratory-based tests and be isolated if necessary. These algorithms could help healthcare providers triage patients with COVID-19 into potentially three groups: the 80% who have mild disease; the 15% who have moderate disease; and the 5% who have severe disease, including those at high risk of mortality. Finally, AI can facilitate the discovery of novel drugs with which to treat COVID-19 [84].
14. Continuing efforts are being made to develop novel diagnostic approaches to COVID-19 using machine learning algorithms. Machine learning-based screening of SARS-CoV-2 assay designs using a CRISPR-based virus detection system (see Cas13 above) is demonstrating high sensitivity and speed. Neural network classifiers have been developed for a large-scale screening of COVID-19 patients based on their distinct respiratory pattern. lso, a deep-learning based analysis system of thoracic CT images, was constructed for automated detection and monitoring of COVID-19 patients over time. Rapid development of automated diagnostic systems based on AI and machine learning can not only contribute to increased diagnostic accuracy and speed but will also protect healthcare workers by decreasing their contacts with COVID-19 patients [85].

Chapter highlights (key points)

1. A novel coronavirus (SARS-CoV-2), probably zoonotically transferred from a bat to a monkey to a human late in 2019, has produced an infectious pandemic of epic proportions labeled COVID-19.
2. As an RNA virus, SARS-CoV-2 is prone towards mutations resulting in variants (e.g., delta, omicron—so far, as of January

2022) which can be more virulent and contagious than the originating novel coronavirus.

3. Messenger RNA (mRNA) vaccines have been developed (in record time) that seem to provide protection of greater than 95% with periodic booster enhancements.
4. An altered mRNA molecule vaccine with an engineered strip of genetic material to mimic the RNA of the virus is injected into the patient causing (actually "tricking") the spiked protein of the virus to induce neutralizing antibodies that destroy the invading coronavirus.
5. Reaching greater than 70% to 80% of the population ("herd immunity" when a sufficient amount of people are immunized ["R-Naught" $R0 < 1$]) requires comprehensive vaccination, comprehensive testing, masks, and social distancing, along with supplemental protection (boosters) against subsequent spread.
6. Diagnostic testing including antibody testing (to detect active or past infection), PCR antigen testing (to detect active infection), and the gold standard, genetic sequencing to identify the code of the invading virus or any variants.
7. Besides essential vaccination (prevention), antiviral agents to treat infections (most effective early) have been developed using monoclonal antibodies (e.g., Regeneron), convalescent plasma, and modified antiviral drugs (e.g., Remdesivir, Paxlovid, etc.). In late stages, strong corticosteroids (e.g., dexamethasone) have demonstrated some value (but limited and not adequate in some advanced cases).
8. Sadly, but not surprising, theories have been advanced by unqualified sources promoting untested medications (e.g., hydroxychloroquine), even dangerous drugs (e.g., Ivermectin) which desperate or naïve people grasp as "magic bullets."
9. A bright spot regarding COVID-19 (if not the light at the end of the tunnel) is the intense scientific research which is producing new drugs and technologies including new methods of RNA screening of viruses, new vaccines (to address potential variants), new genetic procedures (e.g., CRISPR-Cas13), as well as sophisticated AI immunoinformatics (computational immunology) and precision medicine strategies.
10. There are estimated to be over 380 trillion (10^{38}) viruses on planet earth. It doesnot take much imagination to realize that we will be living with infectious pandemics for a long time to come. Let us hope that perfidious politicians step aside, that humans do what's right, and that we all pray for science to guide us on a safe path forward.

References

1. *Principles of epidemiology in public health practice* . Center for

Disease Control and Prevention; May 18, 2012.
2. Piret J, Boivin G. Pandemics throughout history. *Front Microbiol* . January 15, 2021;11:631736 2021 [Published].
3. Hackett K.M. *New polio cases confirmed in five countries* . Precision Vaccinations; September 4, 2021.
4. *Major epidemics of the modern era 1899 – 2021* . Council on Foreign Relations; June 25, 2021.
5. *Global HIV/AIDS overview* . HIV.gov; 2021.
6. Pride D. The viruses Inside You. *Sci. Am. December* . 2020;323(6):46–53. doi: 10.1038/scientificamerican1220-46.
7. *HIV treatment: the basics* . August 16, 2021. ContactUs@HIVinfo.NIH.gov.
8. *What are HIV and AIDS* . June 5, 2020. ContactUs@HIVinfo.NIH.gov.
9. *COVID-19 coronavirus pandemic* . Worldometer; April 2, 2021 Last updated.
10. *Coronavirus COVID-19 global cases by the center for systems science and engineering (CSSE)* . Johns Hopkins University; March 27, 2021.
11. Ortaliza J, Orgera K, Twitter K.A, et al. *COVID-19 continues to be a leading cause of death in the U.S. in September 2021* . KFF Health & Wellbeing; October 3, 2021.
12. Cui J, Li F, Shi Z.L. Origin and evolution of pathogenic coronaviruses. *Nat Rev Microbiol* . 2019;17(B):181–192.
13. David C, Fajgenbaum D.C, June C.H. Cytokine storm. *N Engl J Med* . December 3, 2020;383:2255–2273 2020.
14. Fan Wu F, Zhao S, Yu B, et al. A new coronavirus associated with human respiratory disease in China. *Nature* . February 3, 2020;579:265–269.
15. Wang S.F, Chen K.H, Chen M, et al. Human-leukocyte antigen class I Cw 1502 and class II DR 0301 genotypes are associated with resistance to severe acute respiratory syndrome (SARS) infection. *Viral Immunol* . 2011;24(D):421–426.
16. Zhao J, Zhao J, Mangalam A.K, et al. Airway memory CD4(+) T cells mediate protective immunity against emerging respiratory coronaviruses. *Immunity* . 2016;44(E):1379–1391.
17. Long Q, Liu B, Deng H, et al. Antibody responses to SARS-CoV-2 in patients with COVID-19. *Nat Med* . 2020;26:845–848.
18. Woodward Davis A.S, Roozen H.N, Dufort M.J, et al. The human tissue-resident CCR5(+) T cell compartment maintains protective and functional properties during inflammation. *Sci Transl Med* . 2019;11(521):12 Fan.
19. Zhou P, Yang X.-L, Wang X.-G, et al. A pneumonia outbreak

associated with a new coronavirus of probable bat origin. *Nature* . 2020:1–4.
20. Collins F. *Genomic study points to natural origin of COVID-19* . NIH Director's Blog; March 26, 2020.
21. Dolan L. *8 big cats have tested positive for coronavirus at the Bronx Zoo* . CNN; April 23, 2020.
22. Hobbs E.C, Reid T.J. Animals and SARS-CoV-2: species susceptibility and viral transmission in experimental and natural conditions, and the potential implications for community transmission. *Transbound Emerg Dis* . July, 2021;68(C):1850–1867.
23. Klhůfek J. The role of angiotensin-converting enzyme 2 in the pathogenesis of COVID-19: the villain or the hero? *Acta Clin Belg* . 2020;77(1) 211–18.
24. Cao Y, Li L, Feng Z, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-137 CoV-2) receptor ACE2 in different populations. *Cell Discov* . 2020;6:1–4.
25. Cao Y, Li L, Feng Z, et al. Comparative genetic analysis of the novel coronavirus (2019-nCoV/SARS-137 CoV-2) receptor ACE2 in different populations. *Cell Discov* . 2020;6:19 Zhou.
26. Zeberg H, Pääbo S. The major genetic risk factor for severe COVID-19 is inherited from Neanderthals. *Nature* . 2020;587:610–612.
27. Dugan H.L, Stamper C.T, Li L, et al. Profiling B cell immunodominance after SARS-CoV-2 infection reveals antibody evolution to non-neutralizing viral targets. *Immunity* . 2021;54(6):1290–1303.
28. Wang E.Y, Mao T, Klein J, et al. Diverse functional autoantibodies in patients with COVID-19. *Nature* . 2021;595:283–288.
29. Wilson F.P. *The seven symptoms that best predict COVID* . Medscape; September 28, 2021.
30. Huang C, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* . 2020;395:497–506.
31. Glück T. *Association of comorbidities with COVID-19 outcomes* . NEJM Journal Watch; April 1, 2020.
32. Fox S.E, Li G, Akmatbekov A, et al. Unexpected features of cardiac pathology in COVID-19 infection. *Circulation* . 2021;142 doi: 10.1161/Circulationaha.120.049465 1123–25.
33. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* . July 21, 2020;395(10229):1054–1062 2020 Mar 28.

34. Pletz M.W, Blasi F, Chalmers J.D, et al. International perspective on the new 2019 American thoracic society/ infectious diseases society of America community-acquired pneumonia guideline: a critical appraisal by a global expert panel. *Chest* . November, 2020;158(D):1912–1918.
35. Kass D.A. COVID-19 and severe obesity: a big problem? *Ann Intern Med* . August 12, 2020 doi: 10.7326/M20-5677.
36. Chau C.H, Strope J.D, Figg W.D. COVID-19 clinical diagnostics and testing technology. *Pharmacotherapy* . August, 2020;40(8):857–868.
37. Yeoh Y.K, Zuo T, Lui G.C, et al. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. *Gut* . 2021;70:698–706.
38. Behrmann O, Spiegel M. COVID-19: from rapid genome sequencing to fast decisions. *Lancet Infect Dis* . 2020;20(11):1218.
39. *Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19)* . NIH: National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases; February 16, 2021.
40. *Interim clinical guidance for management of patients with confirmed coronavirus disease (COVID-19)* . NIH: National Center for Immunization and Respiratory Diseases (NCIRD), Division of Viral Diseases; February 16, 2021:8 Worldmeter.
41. Weinreich D.M, Sivapalasingam S, Norton T, et al. *) REGEN-COV antibody combination and outcomes in outpatients with covid-19* . NEJM; September 29, 2021.
42. FDA NEWS RELEASE, . *Coronavirus (COVID-19) update: FDA authorizes monoclonal antibodies for treatment of COVID-19* . November 21, 2020.
43. Radcliffe S. *Monoclonal antibody treatment for COVID-19: effectiveness, cost, and more* . Healthline; August 25, 2021.
44. Terry M. *Vir biotech IDs two antibodies that could Be effective in preventing and treating COVID-19* . BioSpace; March 25, 2020. .
45. Chen P, Nirula A, Heller B, et al. SARS-CoV-2 neutralizing antibody LY-CoV555 in outpatients with covid-19. *N Engl J Med* . January 21, 2021;384(3):229–237.
46. Brouwer P.J.M, Caniels T.G, Van der Straten K, et al. Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability. *Science* . August 7, 2020;369(6504):643–650.
47. Johnson R.M, Vinetz J.M. Dexamethasone in the management of covid-19. *BMJ* . July 3, 2020;370:m2648.
48. Burki T.K. The role of antiviral treatment in the COVID-19

pandemic. *Lancet* . February 2022;10(121–220) e11–2.
49. Paxlovid fact sheet for health care providers. Accessed January 11, 2022. https://www.fda.gov/media/155050.
50. Molnupiravir fact sheet for health care providers. Accessed January 11, 2022. https://www.fda.gov/media/155054.
51. Beigel J.H, Tomashek K.M, Dodd L.E, et al. Remdesivir for the treatment of Covid-19—final report. *N Engl J Med* . November 5, 2020;383:1813–1826.
52. Cavalcanti A.B, Zampieri F.G, Rosa R.G, et al. Hydroxychloroquine with or without azithromycin in mild-to-moderate covid-19. *NEJM* . July 23, 2020 doi: 10.1056/NEJMoa2019014.
53. Popp M, Stegemann M, Metzendorf M.I, et al. Ivermectin for preventing and treating COVID-19. *Cochrane Database Syst Rev* . July 28, 2021;7(7):CD015017.
54. COVID-19 Treatment Guidelines, . Antiviral drugs that are approved or under evaluation for the treatment of COVID-19. https://www.covid19treatmentguidelines.nih.gov/on.
55. Su S, Du L, Jiang S. Learning from the past: development of safe and effective COVID-19 vaccines. *Nat Rev Microbiol* . 2021;19:211–219.
56. Jackson L.A, Anderson E.J, Rouphael N.G, et al. An mRNA Vaccine against SARS-CoV-2 - Preliminary Report. *N Engl J Med* . November 12, 2020;383(20) 1920–31.
57. Supek F, Lehner B, Lindeboom R.G.H. To NMD or not to NMD: nonsense-mediated mRNA decay in cancer and other genetic diseases. *Trends Genet* . July, 2021;37(7):657–668.
58. *NIH vaccine research center leads the way to safe* . effective COVID-19 vaccines; 2021.
59. Ibid. NIH. 58.
60. Aquino-Jarquinab G. Recent progress on rapid SARS-CoV-2/COVID-19 detection by CRISPR-Cas13-based platforms. *Drug Discov Today* . August, 2021;26(8):49.
61. Ibid. Jackson. 51.
62. Orlowski E.J.W, Goldsmith D.J.A. Four months into the COVID-19 pandemic, Sweden's prized herd immunity is nowhere in sight. *J R Soc Med* . August, 2020;113(8):292–298.
63. Bergstrom C.T, Dean N. *What the Proponents of 'Natural' Herd Immunity Don't Say Try to reach it without a vaccine, and millions will die* . New York Times; May 1, 2020.
64. Press Release, . *Decoding the human immune system* . Human Vaccines Project; February 13, 2019.

65. Soto C, Bombardi R.G, Branchizio A, et al. High frequency of shared clonotypes in human B cell receptor repertoires. *Nat vol* . February 13, 2019;566:398–402.
66. Ibid. *Human Vaccines Project*. 62.
67. Niño M.D, Hearne B.N, Cai T. Trajectories of COVID-19 vaccine intentions among U.S. adults: the role of race and ethnicity. *SSM - Populat Health* . 2021;15:100824. doi: 10.1016/j.ssmph.100824.
68. Oli A.N, Obialor W.O, Ifeanyichukwu M.O, et al. Immunoinformatics and vaccine development: an overview. *ImmunoTargets Ther* . 2020;26:13–30.
69. Senior A, Jumper J, Hassabis D, et al. *AlphaFold: using AI for scientific discovery* . March 25, 2020 arXiv.org > cs > arXiv:2003.11336vol. 1.
70. Collins F. Whole-genome sequencing plus AI yield same-day genetic diagnoses. NIH Director's Blog; May 7, 2019. NIH.gov.
71. Gerson M. *Six takeaways from covid-19 that could shape our future. Washington Post* . February 18, 2021.
72. Wu J. How artificial intelligence can help fight coronavirus. Forbes Cognitive World; March 19, 2020.
73. Zhang L, Wang D.C, Huang Q. Significance of clinical phenomes of patients with COVID-19 infection: a learning from 3795 patients in 80 reports. *Clin Transl Med* . April 4, 2020;10(1):28–35. doi: 10.1002/ctm2.17.
74. Ong E, Wong M.U, Huffman A, He Y. COVID-19 coronavirus vaccine design using reverse vaccinology and machine learning. *Preprint bioRxiv* . March 21, 2020 2020;2020.03.20.000141.
75. Chen J, Li K, Zhang Z, et al. *A survey on applications of artificial intelligence in fighting against COVID-19* . July 4, 2020 arXiv:2007.02202v2.
76. Alimadadi A, Aryal S, Manandhar I, et al. Artificial intelligence and machine learning to fight COVID-19. *J/Physiolgenom* . April 3, 2020 108.252.096.178.
77. Cartelle Gestal M, Dedloff M.R, Torres-Sangiao E. Computational health engineering applied to model infectious diseases and antimicrobial resistance spread. *Appl Sci* . June 18, 2019;9(12):2486. doi: 10.3390/app9122486.
78. https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6.
79. Joseph T, Wu J.T, Leung K, Leung G.M. Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *Lancet* . February 29,

2020;395(10225):P689–P697.
80. Zixin H, Qiyang G, Shudi L, et al. *Forecasting and evaluating intervention of covid-19 in the world* . March 22, 2020 arXiv:2003.09800 [q-bio.PE].
81. Heaven W.D. *AI could help with the next pandemic—but not with this one* . MIT Technology Review; March 12, 2020.
82. Waleed A, Preety S, Gupta B.G. Review on machine and deep learning models for the detection and prediction of Coronavirus. *J Matpr* . June 23, 2020;06:245.
83. Maghdid H.S, Ghafoor K.Z, Sadiq A.S, et al. *A novel AI-enabled framework to diagnose coronavirus COVID 19 using smartphone embedded sensors: design study* . May 30, 2020 doi: 10.48550/arXiv.2003.07434 arXiv.org > cs > arXiv:2003.07434..
84. Ting D.S.W, Carin L, Dzau V, et al. Digital technology and COVID-19. *Nat Med* . March 27, 2020 doi: 10.1038/s41591-020-0824-5.
85. Mei X, Lee H, Diao K, et al. Artificial intelligence–enabled rapid diagnosis of patients with COVID-19. *Nat Med* . 2020;26:1224–1228.

Epilogue

So, just what is “the paradox of the immune system?” As you have probably concluded by now, the “paradox” is actually a collection of paradoxes or would-be contradictions, inconsistencies, indeed, even mysteries of medical and healthcare science involving the immune system. Just to list some (as I did in the Preface), but not all that I tried to identify throughout the book (sometimes too often, I'm sure), they include

- Self versus nonself;
- Innate versus adaptive immunity;
- Adaptive immunity as a friend and foe;
- Our “best friend and worst enemy”;
- Immunity's regulated and dysregulated systems;
- Health protection and health threat;
- Dangerous versus benign nonself and the toll-like receptor (TLR) “sentry”;
- Acute inflammation healing and ulceration;
- Acute versus chronic inflammation;
- Accumulation of immune (cellular and humoral) substances in tissue;
- Tumor necrosis factor (TNF-α) inflammatory and antiinflammatory effects;
- Self versus self (autoimmunity);
- Autoimmunity (“the mother of all immune system paradoxes”);
- Female versus male predilections to autoimmune diseases and cancers;
- Rogue B-cell attacking self;
- Epitope spreading;
- The role of the X chromosome and miRNA in males versus females;
- Immunosuppressive agents as therapeutics and as threats;
- The immune system and COVID-19 (the infection's best friend and worst enemy).

As you have learned while reading this book, this is a rather formidable list (perhaps a bit confusing) and it only scratched the surface of the immune system puzzles. Actually, the science of immunology is growing every day. My greatest challenge and frustration during the past year that I have spent writing

this book has been trying to keep up with the deluge of new information being produced and published on a daily basis. I can only hope the book provides a contemporaneous foundation and framework upon which you can build a better understanding of the complexities of this enigmatic science that simultaneously protects us and threatens us (that will be the last paradox I quote—I promise).

Because of the torrent of information, I had to take some liberties uncommon in a scientific discourse. I eliminated erudite dissertations on each element of the immune system (I'll bet you do not believe that, but it is true). Rather, I tried to state the basic biology essential to understanding immunology (and related genetics) without elaborating on the excruciating details presented in the literature. Mostly, I tried to package the science in a comfortable, casual narrative that you the reader could enjoy rather than labor over as in an academic travail. I even inserted some degree of intermittent humor (in case you missed it) to "lighten the load" of the heavy material discussed. No less, as a part of that levity, in Chapter 4 I requested your support and petitioning of NIH for my suggested name change from "chronic inflammation" to "*pathomelitis*." I actually do believe there would be some benefit in such a change, but I'm not too sure my grassroots campaign will amount to much. Who knows?

Immunology, autoimmune disease, cancer, immunotherapies and regrettably, pandemics are the kinds of subjects that need a book as an informational foundation upon which one can continue to build. Like I stated above, those building blocks are coming at us at light speed (or a fire hose, the metaphor I used in the Preface). But with them and the continuing advancements in immunotherapies comes a greater understanding of the paradoxes, vagaries and the suffering wrought upon humanity by autoimmune diseases, chronic diseases, cancers and infectious pandemics. That understanding, along with valuable ameliorators always available to all, like proper diet, physical exercise, stress reduction, and certainly, attention to our environment (our "climatinome" – a little more neologism to add to my "*pathomelitis*") are all collectively so meaningful. While none provide a solution or a "magic bullet," together they give us hope.

The information in the book has made you a well-educated, but no less a student (like all of us) of immunology. Now, it's up to you to maintain and grow that credential for the benefits it will provide for your health and to those whom you may help and care for, patients, family, friends and, humanity at large. In the Introduction to Section 1 of this book, I talked about my love of immunology and genetics. I also made a prognostication (maybe more, a hope) when I said, "Some of my proselytizing about the immune system and genetics in healthcare may not mean much to you now, but I would ask you to come back and reread this Introduction after you have read the book (I'll even remind you at the end). By then, I think you may love immunology and genetics as much as I do." I hope I have succeeded.

As we tinker with the immune system, applying immunotherapies, immunogenetic and immunogenomic, gene editing, gene replacement, stem cell transplantation, we are tempted to think about, even aspire to extended life.

Sure, we are beginning to see the occasional 95 years old still jogging or the 100 years old blowing out birthday candles. It makes us feel like, “I've got a shot” and indeed you do. We can pretty much thank our immune system for giving us that hope. But as far as beating the “grim reaper” or immortality, we all pretty much know, “it ain't gonna happen” in most of our lifetimes. Chronic inflammation, autoimmunity, cancer (or “cancering”), and all the other immune-related diseases are all products of “an enemy within us.” The system that defends most of us, most of our lives, is also the inescapable collaborator in our “last dance.” Best we accept the paradox of the immune system by proffering care and empathy to those who suffer its unkind duplicities as we try to enjoy and be thankful for the benefits and protection it provides.

Glossary

A

Abatacept (Orencia) T-cell inhibitor

ACE-2 Angiotensin-converting enzyme protein on the surface of many cell types and receptor site for novel coronavirus spike protein

Acetylcholine Chief neurotransmitter of the parasympathetic nervous system

Acitretin (Soriatane) Retinoid (used in psoriasis)

Acquired immune system Active immune system producing antibodies

Acquired Immunodeficiency Syndrome (AIDS) Active HIV infection

Acquired mutations Change in gene structure causing abnormality in the human organism

Actemra TNF inhibitor

Active immunity Innate and adaptive immunity

Acute Rapid onset, short duration

Acute inflammation Clinical reaction in adaptive immune response

Adalimumab (Humira) Monoclonal antibody drug

Adaptive immune system Acquired, second-level immunity

Adaptive immunity Second level of immunity (acquired immunity)

Adenine (As) Nucleotide base compound in DNA and RNA

Adjuvant chemotherapy Postoperative chemo to reduce risk of cancer recurrence

Adoptive cell transfer therapy (ACT therapy) Treatment of malignant cancers with CAR-T cells

Adventitia Outer most layer of the wall of a blood vessel

Agranulocyte cells Neutrophils, eosinophils, and basophils

Algorithms Rules followed in calculations or other problem-solving operations

All of Us Precision Medicine initiative by the National Institute of Health

Allele Pairs or series of inherited genes on a chromosome that determines hereditary characteristics

Allergens Specific form of antigen that triggers immunoglobin E (IgE)

Allergy Type IV hypersensitivity response

Allograph Transplantation from one donor to another of the same species

AlphaFold AI Google DeepMind system using amino acid sequencing to predict protein structure

Amino acid Building blocks of the large, complex protein molecules

Amino acids Building block molecules of proteins

Aminosalicylates (mesalamine, Asacol HD, Delzicol, others) Antiinflammatory drugs

Anakinra (Kineret) Immunotherapeutic biologic drug

Anamnestic memory Renewed rapid production of an antibody following second or later contact with the provoking antigen or with related antigens.

Anaphylactic shock Life-threatening hypersensitivity reaction

Angiogenesis inhibitors Block production of new blood vessels

Angioplasty Surgical repair or unblocking of a blood vessel,

Angiotensin-converting enzyme (ACE) Controls blood pressure by regulating the volume of fluids in the body. Also binds spike proteins in SARS-CoV-2.

Anthralin Treatment in psoriasis

Anti-anti-idiotype Second antibody in the Idiotype Regulatory Circuit

Antiidiotype First antibody in the Idiotype Regulatory Circuit

Antiinflammatory medications Drugs to treat acute inflammation

Antimetabolites Suppress DNA synthesis

Anti-TNF (tumor necrosis factor) Proinflammatory cytokine

Antibiotic Treatment for bacterial infection

Antibodies Protein produced in response to and counteracting a specific antigen

Antibody Cellular component of the immune response

Antibody-encoding gene Determines how our immune system attempts to protect us against antigens

Anticoagulant medications (e.g., heparin, warfarin) Medication to reduce clotting

Antigen Foreign, nonself-substance or stress

Antigen presenting complex (APC) Antigen bound to a macrophage and T cell

Antigenic determinants Small sites on antigen surface called epitopes

Antinuclear antibody (ANA) Antibodies that can bind to a normal cell nucleus

Antiviral drugs Boost the immune defense to inhibit viral development

Apoptosis Cell's ability to selfdestruct when something goes wrong

Apoptosis inducers Promote apoptotic effects through a variety of mechanisms

Apremilast (Otezla) Treatment of moderate to severe plaque psoriasis

Artificial intelligence (AI) Computer algorithms mimicking human thinking and learning

Aspirin Acetylsalicylic acid (ASA)

Asthma Chronic, long-term condition that intermittently inflames and swells the airways

Atenolol (Tenormin) Beta blocker in treatment of Grave's disease

Atezolizumab (Tecentriq) Monoclonal antibody drug

Atherogenesis Accumulation of cholesterol or plaques in the arteries

Autoantibodies Antibodies generated by a person's own body

Autoantigen Normal bodily constituent against which the immune system produces autoantibodies.

Autoantigenicity Relating to autoantigens

Autoimmune disease Category of immune diseases of unknown origin (originating through selfantigenicity)

Autoimmunity Misdirected immune response that occurs when the immune system attacks the body itself.

Autologous From “one's self”, for example, hematopoietic stem cell

Autologous CAR-T-cell therapy Targeted lymphocytes are then reintroduced to the patient's body through a single infusion to attack tumor cells

Autologous transplantation Healthy stem cells collected from the blood or bone marrow before treatment then given back to the patient after treatment.

Autosomal dominant allele Determine hereditary characteristics

Autosomal recessive allele Two copies of an abnormal gene must be present for the disease or trait to develop

Avelumab (Bavencio) Monoclonal antibody drug

Azathioprine (Azasan, Imuran) Immunosuppressant drug

B

B-cell lymphocytes See nongranular leukocytes

B-memory cell (B_M) Immune cell with an affinity for a particular antigen

Balsalazide (Colazal) Antiinflammatory drug

Baricitinib (Olumiant) Immunotherapeutic DMARD drug

Base compounds Nucleotides Adenine (A), Cytosine (C), Guanine (G), Thymine (T)

Base pair Nucleotide amino acid base compounds on a gene (collectively called the human exome)

Basophils Agranulocyte white blood cell

Belimumab (Benlysta) Monoclonal antibody drug

Bioinformatics The science of collecting and analyzing complex biological data

Biologics Products made from living organisms or contain components of living organisms

Biomarkers Phenotypic features for any measurable quantity or score that can be used as a basis to stratify patients

Biomedical informatics Data used in big data analytics

Bioscience Any branch of natural and life science

Blinatumomab (Blincyto) Monoclonal antibody drug

BlueDot AI-powered algorithm to analyze information that can track over a hundred infectious diseases

Bone marrow transplant Transplanting blood stem cells, which travel to the bone marrow where they produce new blood cells and promote growth of new marrow.

Brachytherapy Radiation therapy is used to treat many types of cancer

Bradykinin Potent endothelium-dependent vasodilators

BRCA1 Cancer gene associated with breast cancer

BRCA2 Cancer gene associated with breast cancer

Budesonide Inhaled steroid used to prevent asthma symptoms

C

C-reactive protein (CRP) Increases with heart disease

Calcineurin inhibitors Immunomodulating agents used in treatment of psoriasis

Calcipotriene Vitamin D analog used in treatment of psoriasis

Calcitriol (Vectical) Vitamin D analog used in treatment of psoriasis

Calor Heat generation during acute inflammation (or fever in chronic inflammation)

Cancer Group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body

Cancering Verb describing mutations leading to cancer

CANTOS Canakinumab Antiinflammatory Thrombosis Outcomes Study

CAR-T cell Chimeric antigen receptor T cells (gene replacement therapy)

Carcinogenesis Cancer causing

Carcinogenesis Series of mutations in an oncogene

Carcinogens Substances capable of causing cancer in living tissue.

Carcinoid tumors Slow-growing cancer that can arise throughout the body

Carcinoma A cancer that starts in the skin or the tissues that line other organs

Cardiovascular disease Diseases relating to heart and blood vessels

Cas13 enzyme Guide RNAs used in CRISPR technique for possible COVID-19

vaccine

Cas9 enzyme Acts as a pair of "molecular scissors" that can cut the two strands of DNA at a specific location in the genome

Caseation Form of necrosis producing cheese mass of tissue

CD (cluster of deviation) Cell surface glycoprotein expressed on leukocytes and other cells relevant for the immune system (CD3, 4, 8, 19, up to 400)

CDC Center for Disease Control

Cemiplimab (Libtayo) Monoclonal antibody drug

Central dogma of molecular biology Protein synthesis; DNA makes RNA, and RNA makes protein

Centromere Point of attachment of two chromatids (on chromosome)

Cerebrovascular disease Diseases relating to the central nervous system and its vasculature system

Certolizumab (Cimzia) Monoclonal antibody drug

Checkpoint inhibitor Monoclonal antibody drug

Checkpoint inhibitors Immunotherapeutic cancer treatment by blocking certain proteins

Chemotactic Orientation or movement of an organism or cell in relation to chemical agents

Chemotaxis Phenomenon whereby somatic cells, bacteria, and other single-cell or multicellular organisms direct their movements in response to certain chemicals in their environment

Chemotherapy Use drugs to stop the growth of cancer cells

Chimeric Organism or tissue that contains at least two different sets of DNA

Chimeric antigen receptor T cells (CAR-T cells) T cells that have been genetically engineered to produce an artificial T-cell receptor for use in immunotherapy

Chromosome Threadlike structure of nucleic acids and protein found in the nucleus of most living cells, carrying genetic information in the form of genes.

Chronic disease Conditions that last 1year or more and require ongoing medical attention or limit activities of daily living or both; for example, heart disease, cancer, diabetes

Chronic inflammation Extended or permanent clinical manifestation of acquired immune disorders; considered the underlying cause of all human disease

Ciprofloxacin (Cipro) Broad-spectrum fluoroquinolone

Cladribine (Mavenclad) Antimetabolite antineoplastic agent

Clinical autoimmune cycle Autoimmune cycle induced by chronic inflammation

Clobetasol (Temovate) A corticosteroid

Cloning Generating a genetically identical copy of a cell or an organism

Clonotypes Unique sequences of nucleotides (DNA base compounds)

Cluster Disease outbreak grouped in a specific place

Comorbidity see Concurrent Medical Conditions

Computational immunology Immunoinformatics

Concurrent Medical Conditions Comorbidity or multimorbidity

Contact tracing Identifying persons exposed to infectious risk

Convalescent plasma (serum) Antibody rich plasma from previously infected victim

Convolutional neural network Trained deep learning algorithm

Core processor CPU unit that executes multiple instructions simultaneously

Corticosteroids Class of antiinflammatory medications

COVID-19 Highly contagious respiratory disease caused by the SARS-CoV-2 virus

CRISPR-Cas9 and 13 acronym for clustered regularly interspaced short palindromic repeats with RNA guides targeting specific spots in the genome associated protein 9 or 13 (gene editing)

Crohn's disease (CD) Autoimmune gastrointestinal inflammatory disease

Cyclooxygenase Enzyme in inflammatory cascade responsible for formation of prostanoids

Cyclosporine (Sandimmune, Neoral, Gengraf) Calcineurin inhibitor

Cystic fibrosis Hereditary disease that affects the lungs and digestive system

Cytogenetics Study of inheritance in relation to the structure and function of chromosomes.

Cytokine Chemical components of the immune system

Cytokine storm Excessive production of cytokines secondary to Type I hypersensitivity reaction or chronic inflammation

Cytokines Substances and chemicals secreted by certain cells of the immune system and have an effect on other cells

Cytosine [Cs] Base nucleic acids that pairs with guanine in DNA

Cytotoxic Toxic to living cells

D

Damage-associated molecular patterns (DAMPs) Accumulation of cellular damage

Deep learning Algorithms in layers to create an artificial neural network (ANN)

Degranulation Mast cell neutralizing process

Demographics Statistical data relating to population and particular groups within it

Dendritic cell Antigen presenting cell (Macrophage, T-cell and antigen)

Deoxyribonucleic acid DNA

Dexamethasone Powerful corticosteroid

Diabetes insipidus An uncommon disorder that causes an imbalance of fluids in the body

Diabetes Mellitus Type 2 (originally, Adult Diabetes) Glucose (sugar) collects in the blood (hyperglycemia) and does not reach the cells

Diabetes Type 1 (originally, Juvenile Diabetes) Autoimmune destruction of the pancreatic beta cells, which is caused by unknown factors

Diapedesis Extravasation of blood cells through the intact walls of the capillaries

Dimethyl fumarate (Tecfidera) Treatment for multiple sclerosis

Diroximel fumarate (Vumerity) Treatment for multiple sclerosis

Disease-modifying antirheumatic drugs (DMARDs) Immunosuppressive drug category

DNA Deoxyribonucleic acid, the carrier of genetic information

DNA base compounds Adenine (A), Cytosine (C), Guanine (G), and Thymine (T)

DNA editing Direct manipulation of DNA sequences in cells

DNA sequencing Determine the order of DNA proteins (nucleotides) in an individual's genetic code

Dolor Pain in the acute inflammatory process

Dominant alleles (AA) Gene that will produce a certain phenotype, even in the presence of other alleles

Double helix DNA molecules made of two twisting, paired strands

Down syndrome Genetic disorder caused by the presence of all or part of a third copy of chromosome 21 (Trisomy 21)

Downregulate Process of reducing or suppressing a response to a stimulus

Duchenne muscular dystrophy Severe type of muscular dystrophy

Ductal carcinoma in situ (DCIS) Breast cancer

Durvalumab (Imfinzi) Monoclonal antibody drug

Dysbiosis Imbalance between the types of organism present in

Dysregulate Abnormal adaptive immune response

Dysregulated Adaptive immune response

E

Eculizumab (Soliris) Monoclonal antibody drug

Edema Abnormal accumulation of fluid or gases in tissue

ELAM Endothelial adhesion molecule (in inflammatory cascade)

Embryology Study of embryos and their development.

Embryonic stem cell (ESC) Pluripotent, undifferentiated stem cell capable of generating all of the body's cell types

Enbrel TNF inhibitor

Endemic Expected level of observable disease found in a community

Endocarditis Inflammation of endocardium (lining of heart chambers and valves

Endogenous Originating from within an organism.

Endothelial leukocytic adhesion molecule ELAM

Endothelial lining Lining of interior surface of blood vessels and lymphatic vessels

Eosinophils Agranulocyte white blood cell common in allergic reaction

Epidemic Widespread occurrence of an infectious disease in a community or country at a particular time

Epidemiology Branch of medicine which deals with the incidence, distribution, and possible control of diseases and other factors relating to health.

Epigenetics Changes in organisms caused by modification of gene expression

Epigenome Chemical modifications to DNA-associated proteins in the cell, which alter gene expression, and are heritable

Epitope spreading Release of selfantigens during a chronic autoimmune or inflammatory response.

Epitopes Small sites on antigen surface (antigen determinants)

Epstein-Barr Virus (EBV) One of the most common human viruses (causes mononucleosis)

Erythrocyte sedimentation rate (ESR, or sed rate) Blood test that detects and monitors inflammation in the body

Escapees 15% of genes that “escape” XCI

Etanercept (Enbrel) Biologic drug (TNF inhibitor)

Eugenics Practice of improving the human species by selectively mating

Exocytosis Active transport in which a cell transports molecules out of the cell

Exome Part of the genome composed of exons

Exon Portion of a gene that codes for amino acids

Exposome Nongenetic exposures that affect human health and disease

Expression Regulated activity of a gene

F

Feedback inhibition Removal of antigen reduces innate immune stimulus

Fever Inflammatory heat (calor) caused by leukocytic pyrogen

Fibroblast Connective tissue cell

Fingolimod (Gilenya) Immunosuppressive drug in treatment of multiple sclerosis

Fluvoxamine Antidepressant drug used as an antiviral

Functio laesa Loss of function secondary to inflammation

G

Gene Basic unit of heredity, a sequence of nucleotides in DNA or RNA that encodes the synthesis of a gene product, either RNA or protein

Gene editing Type of genetic engineering in which DNA is inserted, deleted, modified or replaced in the genome (e.g., CRISPR-Cas9)

Gene expression Effect attributed to a particular gene

Gene expression modulation Practice of altering the expression of a gene

Gene mutation Change in base compound sequencing

Gene replacement therapy Applying a piece of DNA in its correct form though a viral vector (CAR-T cell therapy)

Gene sequencing Ordering of base compound pairs (adenine paired with thymine and guanine paired with cytosine).

Gene signature Gene expression or number of RNA molecules they produce

Genetic and hereditary disorders Inherited disorders

Genetic cloning The processes used to create an exact genetic replica of another cell, tissue or organism

Genetic code Nucleotide triplets of DNA and RNA molecules that carry genetic information

Genetic engineering or modification Modification of the characteristics of an organism by manipulating its genetic material

Genetic testing Tests to identify changes in chromosomes, genes, or proteins

Genome An organism's complete set of DNA, including all of its genes

Genome-wide association studies (GWAs) research to associate specific genetic variations with particular diseases

Genomic medicine Clinical science that attempts to build individual strategies for diagnostic or therapeutic decision-making

Genomics Study of genes and their functions

Genotype Organism's complete set of genetic material

Germ cell tumors Growths that form from reproductive cells

Germline genetic modification Ability to change an organism's DNA

Giant-cell arteritis Inflammatory disease affecting the large blood vessels of the scalp, neck, and arms

Glatiramer acetate (Copaxone, Glatopa) Immunomodulator medication used to treat multiple sclerosis

Gliptins (DPP-4 inhibitors) Work by preventing the breakdown of a naturally occurring hormone called GLP-1 in type 2 diabetes

GLP-1 agonists For type 2 diabetes, act similarly to the natural hormone GLP-1 (see gliptins)

Goeckerman therapy Coal tar treatment with UVB light therapy

Golimumab (Simponi) Monoclonal antibody drug

Google's DeepMind Health Precision medicine program

Granular leukocytes Eosinophils, neutrophils, and basophils

Granuloma Collection of inflammatory cells

Graphic processing units (GPUs) Specialized electronic circuit designed to rapidly manipulate and alter memory to accelerate the creation of images

Grave's disease Autoimmune disorder that causes hyperthyroidism, or overactive thyroid

Guanine [Gs] Base compound of DNA and RNA

Guardian of the genome p53 protein (prevents mutations from being passed on to subsequent cells)

Guillain-Barre syndrome (GBS) Disorder in which body's immune system attacks nerves

H

Haploid strands Single set of chromosomes

Helicobacter pylori (H. pylori) Risk of stomach cancer

Helix Corkscrew configuration—double in DNA and single in RNA molecules

Hematopoietic stem cell therapy Stem cell transplantation procedure

Heparin Substance that slows the formation of blood clots

Hepatitis B Virus and Hepatitis C Virus (HCV) Viruses that increase the risk of liver cancer

Herd immunity Protection from infectious disease that occurs when a sufficient percentage of a population has become immune to an infection

Heredity The passing on of physical or mental characteristics genetically from one generation to another

Heterozygous One recessive and one dominant allele

Heuristic Trial and error, intuitive or “rule of thumb”

Histamine Vasodilator in Type IV allergic reaction

Histopathology Study of changes in tissues caused by disease

Hives See Urticaria

Hodgkin's lymphoma Highly curable malignancy of lymphatic tissues

Homeostasis A relatively stable equilibrium between interdependent elements, especially as maintained by physiological processes

Homograph Transplantation from one donor to another of the same species (see allograph)

Homozygous Two recessive alleles

Human Genome Project Complete mapping of the human DNA sequencing

Human Immunodeficiency Virus (HIV) Risk of Kaposi sarcoma, lymphomas (including both non-Hodgkin lymphoma and Hodgkin disease), and cancers of the cervix, anus, lung, liver, and throat

Human leukocytic antigen (HLA) Group of related proteins encoded by the major histocompatibility complex (MHC Class 1 and 2) gene complex

Human Papillomaviruses (HPVs) Viruses that increase risk of all cervical cancers and penile cancers;

Human T-Cell Leukemia/Lymphoma Virus Type 1 (HTLV-1) Viruses that increase risk of adult T-cell leukemia/lymphoma (ATLL);

Human Vaccines Project Combining systems biology with artificial intelligence to understand one of the greatest human immune systems

Humoral Blood-related serum and fluids that carry WBCs, B and T lymphocytes, and chemical components like cytokines

Hybridoma technology Method for producing large amounts of identical antibodies

Hydrocortisone Corticosteroid

Hydroxychloroquine (Plaquenil) Biologic used unsuccessfully as an antiviral against novel coronavirus but quite successfully as an antihelminth

Hydroxyurea (Droxia, Hydrea) Treatment for psoriasis

Hygiene hypothesis Continuing human effort to “clean” everything

Hyperplasia Increase in cell number

Hypersensitivity response Allergic Type IV IgE response

Hypertrophy Increase in the size of cells

Hypothalamic–pituitary–adrenal (HPA) axis Responsible for cortisol production

I

Ibuprofen Nonsteroidal antiinflammatory drug (NSAID)

Idiotype A set of antigen-binding sites which characterizes the antibodies produced by a particular clone of antibody-producing cells.

Idiotype network theory (INT) B-cell idiotype circulatory loop

Idiotype-Anti-idiotype Regulatory Circuit (or Loop) A regulatory network, which is based on Idiotype–anti-Idiotype B-cell cloning

Idiotypic epitopes Genetically cloned antibodies with unique profiles from B-cell idiotype circulatory loop

Immune synapse MHC receptors activate and bind the individual's T_H cells to the antigens and the macrophage's surface receptors

Immune system Complex network of cells, tissues, and organs serving as primary defense system of the human body

Immunity Ability of the human body to recognize self versus nonself

Immunize Stimulating neutralizing antibodies to the source of an infection.

Immuno-oncology Study and development of treatments using the immune system to fight cancer

Immunocompromised Impaired immune system

Immunodeficiency Lack of immune response to antigen

Immunogenetics Branch of medical genetics that explores the relationship between the immune system and genetics.

Immunogenomics Adding, for each of us, the millions of uniquely randomized T- and B-cell receptor genes that encode our immune repertoires

Immunoglobulin E (IgE) Hypersensitivity, allergic immune reaction

Immunoinformatics Bioinformation of immune system

Immunology Study of the structures and functions of the immune system

Immunome Set of genes and proteins that constitute the immune system

Immunomics Immune system regulation and response to pathogens using genome-wide approaches

Immunomodulators Non-specific drug categories that suppress or stimulate the immune system

Immunopathology Study of the immune systems response to disease

Immunopharmacology Dealing with drugs acting on the immune system and with the pharmacological actions of substances derived from the immune system

Immunosenescence Immune system regarding aging

Immunosuppression Decreased (suppressed) immune system

Immunotherapeutics Biologic drugs, agents, and procedures related to the immune system

In silico Research conducted by means of computer modeling or computer simulation in the same group are more similar to each other than the points in the other groups

Incidence Frequency of new occurrences of a medical disorder in the studied population at risk

inDelphi Algorithm to predict DNA repairs through Cas9

Independent variables Variable (often denoted by x) whose variation does not depend on that of another.

Induration Hardening due to chronic edema

Infectious Disease Vulnerability Index AI modeling studies of "nowcasting" and forecasting COVID-19 disease activity throughout the world

Infiltration Diffusion or accumulation (in a tissue or cells) of foreign substances or in amounts in excess of the normal

Inflammaging Inflammatory process as a product of aging

Inflammation Acute or chronic clinical response of the acquired immune

response characterized by reddened (“rubor”), hot (“calor”), swelling (“tumor”), and pain (“dolor”)

Inflammatory bowel disease (IBD) Autoimmune inflammatory disease of the colon

Inflammatory cascade Pharmacodynamic development wherein the human immune system has not yet evolved a specific response

Infliximab (Remicade) Monoclonal antibody drug

Innate (*aka* natural) immune response Immediate nonspecific defense mechanism in response to an antigen

Innate immune system Natural (healthy) defense system of the body

Insulin Hormone produced in the pancreas by the islets of Langerhans, which regulates the amount of glucose in the blood

Interferon Immune system cytokine

Interleukins Immune system cytokine

Ipilimumab (Yervoy) Monoclonal antibody drug

Isoantigens Histocompatibility (HLA) gene

itis Suffix for inflammation

Ivermectin Antiparasitic drug ysed as an antiviral

Ixekizumab (Taltz) Monoclonal antibody drug

K

Kahler disease Damage and weakened bones in Multiple Myeloma

Karyotype Overall number and shape of all your chromosomes

Kynurenine pathways Regulators of cancer immunity

L

Leflunomide (Arava) Pyrimidine synthesis inhibitor

Lefluomide See DMARD

Leukemia A cancer of bone marrow; creates abnormal WBCs

Leukocytes White cells that help the body fight bacteria and infection

Leukocytic pyrogen Heat producing mediator produced by interleukin

Ligand A molecule that binds to another molecule

Lipoxygenase Enzymes that catalyze fatty acids in inflammatory cascade

Lonpinavir Antiviral protease inhibitor use for HIV and with Paxlovid

Lymphatic system Network of tissues and organs that help rid the body of toxins, waste, and other unwanted materials

Lymphocytes (T_H,T_S,T_C,T_M and B, B_M) Cellular component of the immune system

Lymphoma Cancers of the immune system causing abnormal lymphocytes to become lymphoma cells

Lysing Outer boundary or cell membrane is broken down

M

Machine learning Principal learning process in AI

Macrophage Large phagocytic white blood cell

Major histocompatibility complex (MHC Class 1 and 2) genes Genetic system that allows large proteins in immune system cells to identify compatible or foreign proteins (Class 1 with T_C CD8 receptors and Class 2 with T_H CD4 receptors)

Malignant Cancer

Masking effect Steroid reduction of inflammatory symptoms

Melanoma Pigmented malignant tumor

Mendelian disorders Mutation at a single genetic locus

Mercaptopurine (Purinethol, Purixan) Immunosuppressant in treatment of IBD

Merkel cell carcinoma Rare type of skin cancer as flesh or blue coloration on face (neuroendocrine carcinoma)

MERS-CoV Middle east respiratory virus

Messenger RNA (mRNA) Transcribes genetic information from DNA as a sequence of bases is transferred to a ribosome.

Metastasis Spreading of cancer cells

Metastatic cancer Disseminated cancer

Methotrexate (Trexall, Xatmep, others) Purine metabolism inhibitor, immunosuppressant in IBD (See DMARDs)

Methylprednisolone (Medrol) Corticosteroid

Metoprolol (Lopressor, Toprol-XL) Bet blocker used in treatment of Grave's disease

Metronidazole (Flagyl) Antibiotic used in IBD

Microbiome Genetic material of all the microbes—bacteria, fungi, protozoa, and viruses—that live on and inside the human body

Microbiota Microorganisms found in a particular habitat (in microbiome)

Microchimerism Presence of genetically distinct cells in an individual

microRNA Associated with the X chromosome

Moderna Vaccine manufacturer (mRNA-1273)

Molecular biology Branch of biology that deals with the structure and function of the macromolecules (e.g., proteins and nucleic acids) essential to life.

Molecular genetic tests Gene tests

Molecular genetics Molecular biology of genetics

Molecular radiotherapy Targeted radionuclide therapy

Molecularly targeted therapies Cancer treatment

Molnupiravir Antiviral nucleoside analogue

Monoclonal antibodies Immune system modulators

Monocytes See nongranular leukocytes

mRNA Messenger ribonucleic acid

Multiomics Genotype-phenotype data through genome-wide association studies (GWAS)

Multimorbidity see Concurrent Medical Conditions

Multiple myeloma Cancers that begin in plasma cells and form tumors in bone marrow (see Kahler disease)

Multiple sclerosis (MS) Autoimmune demyelinating disease (encephalomyelitis disseminate)

Multisystem inflammatory syndrome in children (MIS-C) Chronic inflammation in multiple organ systems, especially in children

Mutation Changing of the structure of a gene, resulting in a variant form that may be transmitted to subsequent generations, caused by the alteration of single base units in DNA, or the deletion, insertion, or rearrangement of larger sections of genes or chromosomes; see gene mutation

Myasthenia gravis (MG) Autoimmune disease characterized by weakness and rapid fatigue of any of the muscles under your voluntary control

Mycophenolate (Cellcept) Immunosuppressant to treat myasthenia gravis

Myocarditis Inflammation of heart muscles (myocardium)

N

Nadolol (Corgard) Beta blocker to treat Grave's disease

Naproxen A nonsteroidal antiinflammatory drug (NSAID)

National Cancer Institute U.S. government's principal agency for cancer research

National Institute of Health (NIH) U.S. Department of Health and Human Services, NIH is the largest biomedical research agency in the world

Natural immune system Innate immune system

Natural killer [NK] cells WBC immune cell that has granules (small particles) with enzymes that can kill tumor cells or cells infected with a virus

Naught point Null point for infectious spreading (R_0)

Necrosis Death of body tissue

Neoadjuvant chemotherapy Treatment given as a first step to shrink a tumor before the main treatment

Neoplasm A new and abnormal growth of tissue in some part of the body, especially as a characteristic of cancer

Neoplastic Relating to a neoplasm or neoplasia

Neostigmine (Bloxiverz) Cholinesterase inhibitors in treatment of myasthenia gravis

Neuroendocrine tumors See Merkel cell carcinoma

Neutralizing antibodies Defends a cell from a pathogen or infectious particle by neutralizing any effect it has biologically

Neutrophils Type of white blood cell that helps heal damaged tissues and resolve infections

Next-generation sequencing or next-gen sequencing (NGS) A high-throughput method used to determine a portion of the nucleotide sequence of an individual's genome; see Sanger Method

Nivolumab (Opdivo) Monoclonal antibody drug

Non-Hodgkin lymphoma cancer that starts in lymphocytes (WBCs)

Non-specific therapies Generalized immunosuppressive and immunomodulating (suppressing or stimulating) therapies

Nonself Antigen

Normal flora Microorganisms that live on another living organism without causing disease

Novel coronavirus (nCoV) A new strain of coronavirus that has not been previously identified in humans

NSAIDs Nonsteroidal antiinflammatory drugs; see aspirin, ibuprofen, naproxen

Nuclear factor-kappa B (NF-κB) Transcription factor involved in inflammatory and immune responses

Nucleic acids Complex organic substance present in living cells, especially DNA or RNA, whose molecules consist of many nucleotides linked in a long chain

Nucleotide bases Adenine (As), thymine (Ts), guanine (Gs), and cytosine (Cs)

O

Olsalazine (Dipentum) Antiinflammatory drug

Oncoevolution Cell transformation into a neoplastic cell

Oncogene A gene that can transform a normal cell into a neoplastic cell

Oncogenesis Process through which healthy cells become transformed into cancer cells

Oncology Study and treatment of cancer and tumors

Opsinization Altering of bacteria by opsonins so as to become more readily and more efficiently engulfed by phagocytes

Organ morphogenesis The biological process that causes a cell, tissue or

organism to develop its shape

Osteoarthritis Protective cartilage that cushions the ends of your bones wears down over time (most common form of arthritis)

Outbreak Sudden rise in expected level of disease

Overshoot Continued infection after R0 Naught

P

p53 Protein that prevents mutations from being passed on to subsequent cells (called “Guardian of the Genome”)

PALB2 Gene for breast cancer

Pandemic A disease prevalent over the whole world

Passive immunity Immunity which results from the introduction of antibodies from another person (e.g., mother to fetus in utero)

Pathogen Microorganism causing disease

Pathogenesis Natural history of a disease

Pathology The bioscience of the causes and effects of diseases, especially the branch of medicine that deals with the laboratory examination of samples of body tissue for diagnostic or forensic purposes

Pathophysiology The disordered physiological processes associated with disease or injury

Paxlovid Antiviral protease inhibitor drug

PCR Polymerase chain reaction viral antigen diagnostic test

PD 1 and 2 Programmed cell death protein inhibitors

PD-L1 Ligand on cancer cell

Pembrolizumab (Keytruda) Monoclonal antibody drug

Peripherals Any external device that provides input and output for the computer

Perivasculitis Inflammation of the adventitia of a blood vessel or a lymphatic vessel or of the tissues surrounding it

Personalized health care Precision health care

Personalized medicine Precision medicine

Pfizer Vaccine manufacturer (BNT162b2)

Phagocyte Free-living one-celled organism that ingests or engulfs other cells or particles

Phagocytize To ingest bacteria or other material

Phagocytosis Process by which certain living cells called phagocytes ingest or engulf other cells or particles

Pharmacodynamics Branch of pharmacology concerned with the effects of drugs and the mechanism of their action

Pharmacoeconomics Branch of health economics which deals with identifying, measuring, and comparing the costs and consequences of pharmaceutical products and services

Pharmacogenetics Study of how people respond differently to drug therapy based upon their genetic makeup or genes

Pharmacogenomics Study how an individual's genome can impact their responses to medication

Pharmacovigilance The practice of monitoring the effects of medical drugs after they have been licensed for use, especially to identify and evaluate previously unreported adverse reactions.

Phenotype How a trait—genotype—shows on your physical body

Phenotype trigger Environmental factors combining with specific genes to produce a clinical manifestation (e.g., cancer in smoking)

Phylogeny Evolution of a species or group

Physical distancing See Social distancing

Pimecrolimus (Elidel) Calcineurin inhibitor used in treatment of psoriasis

Plaquenil Hydroxychloroquine

Plasma Liquid portion of blood (serum)

Plasma cell myeloma See Kahler disease

Plasma cells Fully differentiated B cell that produces a single type of antibody

Plasmapheresis Process in which plasma is separated from the blood cells

Plasmid vector Vehicles used to drive recombinant DNA into a host cell in molecular cloning

Platelets See thrombocytes

Pleiotropic One gene influences two or more

Pluripotent stem cells Cells that can undergo selfrenewal and give rise to all cells of the tissues of the body

Polyarthritis Five or more joints are affected with joint pain

Polydipsia Increased thirst

Polymerase chain reaction (PCR) Molecular test to detects genetic material of virus using a lab technique

Polymorphism Genetic alterations that occur in more than 1 percent of the population

Polymorphonuclear (PMN) A leukocyte with a variable formed nucleus (e.g., neutrophil)

Polyphagia Excessive or extreme hunger

Polyuria Frequent urination

Precision health See precision medicine

Precision medicine Looks at the genetics, environment, and lifestyle of a person in order to select best treatment

Precision Medicine Initiative (PMI) A long-term research project, involving the National Institutes of Health (NIH) and multiple other research centers, which aims to understand how a person's genetics, environment, and lifestyle can help determine the best approach to prevent or treat disease

Predictive analytics Identifying mutations that increase a person's risk

Prednisone Corticosteroid

Prevalence Proportion of persons in a population who have a particular disease or attribute

Preventive mastectomy Preventive (prophylactic) surgical removal of breast at high risk of cancer (e.g., BRCA1, BRCA2, or PALB2 gene)

Pro-inflammatory cytokine Type of signaling molecule that is secreted from immune cells like helper T cells (Th) and macrophages, and certain other cell types that promote inflammation.

Probiotics Microorganism introduced into the body for its beneficial qualities

Progenitor Originating cause

Programmed death (PD) protein Plays a major role in suppressing the immune system during the formation of the PD-1/PD-L1 pathway, which transmits an inhibitory signal to reduce T-cell activity

Prophylactic Preventative

Propranolol (Inderal, InnoPran XL) Beta blocker in treatment of Grave's disease

Propylthiouracil Anti-thyroid medication

Prostaglandins Group of compounds with varying hormone-like effects

Protease Enzyme which breaks down proteins and peptides.

Protein synthesis Process in which cells make proteins (see Central dogma of molecular biology)

Proteoglycan Protein bonded to glycosaminoglycan group

Proteolysis Breakdown by protease of proteins or peptides into amino acids

Proteome Gene protein

Proteomics Biochemistry, functions, and interactions or proteomes within the body

Proto-oncogenes Genes that promote cell growth and cellular division

Protocols Procedure or system of rules governing actions

Psoriasis Autoimmune disease that causes skin disorder whereby skin cells multiply up to 10times faster than normal

Public health branch of medicine dealing with public health, including hygiene, epidemiology, governmental support, and disease prevention

Pus Opaque liquid produced in infected tissue, consisting of dead white blood cells (neutrophils) and bacteria with tissue debris and serum

Pyridostigmine (Mestinon, Regonal) Cholinesterase inhibitor in treatment of myasthenia gravis

R

R-Naught (R_O or RO) Null point for infectious spreading

Radiation therapy Type of cancer treatment that uses beams of intense energy to kill cancer cells.

Radioactive iodine (I-131) Treatment for Grave's disease

Radiogenomics Radiographic image analysis used to predict underlying genotypic traits

Radiography The process or occupation of taking radiographs to assist in medical examinations

Radiomics Information from large datasets of qualitative and quantitative imaging

Recessive Gene is a gene that can be masked by a dominant gene

Recessive alleles (aa) When present on its own will not affect the individual. Recombinant: Genetic material formed by recombination (e.g., recombinant DNA)

Regenerative medicine The process of replacing or “regenerating” human cells, tissues, or organs to restore or establish normal function; see Stem cells

Regression Measure of the relation between the mean value of one variable (e.g. output) and corresponding values of other variables

Regulated immune system Innate (natural) immune system

Remdesivir Antiviral drug that interferes with coronavirus mechanism

Remicade TNF inhibitor

Replacement therapy CAR-T cell replacement therapy

Retinoids Vitamin A based therapy to reduce epithelial growth (in psoriasis)

Rheumatoid arthritis (RA) Common autoimmune disease affecting joints

Rheumatoid factor Immune proteins that can attack healthy tissue

Ribonucleic acid (RNA) Single stranded molecule essential in various biological roles in coding, decoding, regulation and expression of genes

Ribosome A minute particle consisting of RNA and associated proteins found in large numbers in the cytoplasm of living cells

Ritinovir Antiviral drug for HIV and used with Paxlovid

Rituximab (Rituxan, Truxima) Monoclonal antibody drug

RNA Ribonucleic acid, principal role is to act as a messenger carrying instructions from DNA for controlling the synthesis of proteins

RNA sequencing (scRNA-seq) Technique using NGS to reveal the presence and quantity of RNA in a sample at a given moment

Rogue Out of ordinary, or against the rules (e.g., rogue antigen-presenting complex)

Rogue B cell B cells involvement in the development of autoimmunity through epitope spreading

Rubor Redness associated with acute inflammation

S

Salicylic acid Type of phenolic acid

Sanger method Original method for determining the nucleotide sequence of

DNA replaced by “next generation sequencing” (NGS)

Sarcoma Cancers that begin in the bones and in connective tissues

Sarilumab (Kevzara) Monoclonal antibody drug

SARS-CoV-2 Severe acute respiratory syndrome, novel coronavirus

Secukinumab (Cosentyx) Monoclonal antibody drug

Self Anything relating to the body (versus nonself)

Self-recognition To distinguish what is nonself (foreign) from what is self

Sensitivity Ability of a test to correctly identify patients with a disease

Sequences Kind of genetic information that is carried in a particular DNA segment

Seroconversion A change from a seronegative to a seropositive in blood

Serology Study or diagnostic examination of blood serum relative to immune response

Serotype (Ad5) Human species C adenovirus serotype 5 (Ad5) most common viral vector used in clinical studies

Serum See plasma

Signature Single or combined group of genes in a cell with a uniquely characteristic pattern of gene expression

Simponi TNF inhibitor

Siponimod (Mayzent) Treatment for multiple sclerosis

Skin, tears, mucus secretions, and mucus membranes Anatomical features of innate immune system

Small-molecule drugs Target molecules small enough to enter cells easily

Social distancing Maintaining minimum distance between people during epidemic

Somatic cells Any cell of the body except sperm and egg cells

Somatic mutations Genetic alteration acquired by a cell that can be passed to the progeny of the mutated cell in the course of cell division

Specificity Ability of a test to correctly identify people without the disease

Spike protein A protein (S) which protrudes from the envelope of a coronavirus, allowing for entry of the virion into a host cell by binding to an ACE-2 receptor on its surface

Staging Determination of how advanced the cancer is relative to its spreading (metastasis)

Stem cell therapy Use of stem cell transplantation to treat or prevent a disease or condition

Stem cell transplantation Stem cell replacement therapy

Stress antigens Any form of stress producing an immune response

Subgenomic RNA Messengers for protein expression, or to regulate their viral life cycle

Sulfasalazine (Azulfidine) IL-1 and TNF suppressor

Synovectomy Surgical procedure used to treat synovitis and some other conditions that affect the synovium (thin membrane that lines the inside of

certain joints called “synovial joints”)

Synthetic promoters Sequence of DNA that does not exist in nature and which has been designed to control gene expression of a target gene.

Systemic Lupus Erythematosus (SLE) Multisystem, diffuse autoimmune disease attacking healthy tissue and organ systems in many parts of the body

T

T-cell lymphocytes Agranulocyte, WBCs, leukocytes

T-cell transfer therapy type of immunotherapy that makes your own immune cells better able to attack cancer (e.g., CAR-T cell therapy)

T-cytotoxic cell (T_C) Immune cell that can kill certain cells, including foreign cells, cancer cells, and cells infected with a virus

T-helper cell (T_H) Recognizing foreign antigens and secreting substances called cytokines that activate T and B cells

T-memory cell (T_M) Antigen-specific T cells that remain long-term after an infection has been eliminated to support anamnestic response

T-regulatory cell (T_{REG}) Specialized subpopulation of T cells that act to suppress immune response (similar to T_S cell)

T-suppressor cell (T_S) Immune cell that blocks the actions of some other types of lymphocytes, to keep the immune system from becoming over-active

Tacrolimus (Astrograf XL, Prograf, Protopic) Calcineurin inhibitor to treat psoriasis

Target code Fully compiled or assembled program ready to be loaded into the computer

Tazarotene (Tazorac, Avage) See retinoids

Telomere Compacted DNA nucleotides at tips of chromosomes associated with aging

Teprotumumab (Tepezza) Monoclonal antibody drug

Teriflunomide (Aubagio) Treatment of multiple sclerosis

Thioguanine (Tabloid) For treatment of psoriasis

Thrombocytes Platelets aid the formation of blood clots

Thymine (Ts) Nucleic acid base compound of gene

TIDE (for Tumor Immune Dysfunction and Exclusion) Technique called “single-cell RNA sequencing” (scRNA-seq)

TNF-α Tumor Necrosis Factor alpha (TNF alpha), an inflammatory cytokine to monitor vital signs and emergencies

Tocilizumab (Actemra) Monoclonal antibody drug

Tofacitinib (Xeljanz) Only pill of its kind (JAK [Janus kinases] inhibitor) that treats rheumatoid arthritis

Toll-like receptor proteins (TLRs) Surface receptors encoded by major histocompatibility complex (MHC) that allow T cells to distinguish

between self and nonself and even between self and self

Topoisomerase inhibitors Anti-metabolites that suppress DNA synthesis

Toxin delivery molecules Cancer treatment

Transcription Process by which DNA is copied to RNA in protein synthesis

Transcriptomics Expression of the genes' proteins (the proteome)

Transfer RNA (tRNA) Transport amino acids from the cytoplasm of a cell to a ribosome in protein synthesis process

Translation RNA is used to produce proteins in protein synthesis

Transmitter substances Chemicals (cytokines) that produce signals in the innate and adaptive immune responses

tRNA Transfer RNA

Tumor Swelling from edema in inflammation or caused by an abnormal growth of tissue, whether benign or malignant

Tumor Immune Dysfunction and Exclusion See TIDE

Tumor necrosis factor Multifunctional pro-inflammatory cytokine that plays important roles in diverse cellular events

Tumor suppressor genes Discourage cell growth, or briefly halt the process of DNA repair

Tumorigenic antigens Carcinogens

Type 1 diabetes Autoimmune disease in which very little or no insulin is produced by islets of Langerhans in the pancreas (previously known as juvenile diabetes)

Type I, allergic Immediate, allergic (or anaphylactic) hypersensitivity response

Type II, cytotoxic Hypersensitivity reaction (sometimes referred to as antibody-dependent cell-mediated cytotoxicity [ADCC])

Type III, immune-complex Hypersensitivity reaction mediated by the formation of antigen-antibody aggregates called “immune complexes”

Type IV, cell-mediated, delayed reaction Involves the activation of phagocytes (pathogen specific), natural killer cells (NK), antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen

U

Ulceration Circumscribed inflammatory often suppurating lesion on the skin or an internal mucous surface resulting in necrosis of tissue.

Uracil Base compound of RNA molecule replaced by thymine in DNA molecule

Urticaria An outbreak of swollen, pale red bumps or plaques (wheals) on the skin that appear suddenly—either as a result of the body's reaction to certain allergens or for unknown reasons; see Hives

Ustekinumab (Stelara) Monoclonal antibody drug

V

Vaccination Treatment with a vaccine to produce immunity against disease; inoculation.

Vaccine Biological agents that elicit an immune response to a specific antigen

Vasculitis Group of disorders that involve inflammation of blood vessels produced by immune system

Variant Alteration in the most common DNA nucleotide sequence

Vasodilation Dilatation of blood vessels

Vaxign-ML AI tool to predict COVID-19 vaccine candidates

Vedolizumab (Entyvio) Monoclonal antibody drug

W

White blood cells (WBCs) or leukocytes Include lymphocytes, granulocytes, monocytes, and macrophages

Whole-exome sequencing (WES) Genomic technique for sequencing all of the protein-coding regions of genes in a genome (known as the exome)

Whole-genome sequencing (WGS) Comprehensive method for analyzing entire genome

X

X chromosome inactivation (XCI) Embryologic transfer from female to male

Y

Yin and yang “All things exist as inseparable and contradictory opposites” as in immunology's self and nonself-proposition

Z

Zoonotic spillover Transmission from animal to human

Index

Note: 'Page numbers followed by "f" indicate figures and "t" indicate tables.'

A

ACE-2. *See* Angiotensin converting enzyme (ACE-2)

Acquired immune system, 229–230

Acquired immunodeficiency syndrome (AIDS), 186

  See also Human immunodeficiency virus (HIV)

Active immunity

  antibody-encoding gene, 16

  cellular attack, 15–16

  chemical/humoral attack, 17–18 , 17f

  first signal, 13–15 , 14f

  regulated immune system, 18–20 , 19f

  regulated to dysregulated, 20–21

Acute inflammation, 26–33 , 74–80

  allergic hypersensitivity responses, 29

  cell-mediated, 30–31

  clinical considerations, 33–38

  cytotoxic hypersensitivity reaction, 30

  delayed reaction, 30–31

  dysregulation, 27–31

  hypersensitivity, 27–31

  immediate hypersensitivity responses, 29

  immune-complex hypersensitivity reaction, 30

  immunopathophysiology, 27–31

  signs, 34–35

  symptoms, 34–35

treatment approaches, 35–38
Adaptive immune system
acute inflammation, *See* Acute inflammation
allergic hypersensitivity responses, 29
cell-mediated, 30–31
chronic inflammation, *See* Chronic inflammation
clinical considerations, 33–38
cytotoxic hypersensitivity reaction, 30
delayed reaction, 30–31
dysregulation, 27–31
hypersensitivity, 27–31
immediate hypersensitivity responses, 29
immune-complex hypersensitivity reaction, 30
immunopathophysiology, 27–31
signs, 34–35
symptoms, 34–35
treatment approaches, 35–38
Adenine (As), 46–47 , 47f–48f , 51 , 53f
base compound, 231
nucleotide, 229–230
Adjuvant chemotherapy, Cancer, 162
Adoptive cell transfer therapy (ACT therapy), 165
CAR-T cell transfer, 165–168
CAAR-T cell transfer, 165
Advancing adaptive immunity, 73–74
Algorithms, 62–63 , 141–145 , 211 , 218
All of Us, 3 , 33–34 , 82 , 151
precision medicine, 57
Allele, 48–51
heredity, 46 , 48 , 51 , 59
Allergic hypersensitivity responses, 29 , 31–33
Allergy, 18 , 29 , 207
type I allergic hypersensitivty response, 73–74
AlphaFold, 211
Google DeepMind, 211

Amino acid, 51–54 , 53f , 211
Anamnestic memory
  T memory cells, 140
  B memory cells, 193
Anaphylactic shock, 29
Angiotensin-converting enzyme (ACE), 120–121
Anti-idiotype, 26 , 164–165

Anti-inflammatory medications,
  immunotherapeutics, 118 , 126 , 199–204
Antibody testing, 197
Antibody-encoding gene, 16 , 60 , 102–103
Antigen, 72 , 86
Antigen presenting complex (APC), 11–12 , 12f
  dendritic cell, 11 , 12f , 20
  immune synapse, 11 , 13–15
Antibody testing, 197
Antinuclear antibody (ANA), 110–111
Antiviral drugs
  Hydroxychloroquine (Plaquenil), 129 , 203–204
  Ivermectin, 204
  Molnupiravir, 203
  Paxlovid, 203
  Remdesivir, 203
Apoptosis, 30–31 , 55–56 , 76 , 78 , 99 , 103–104 , 152 , 156
Artificial intelligence (AI)
  algorithms, 41–42 , 63 , 215–218
  deeplearrning
  machine learning, 57 , 138–139 , 139f , 141–145 , 169–175 , 215–218
Asthma, 21–22 , 29 , 80 , 120 , 130 , 193 , 204
Autoantibodies, 21–22 , 110–111 , 115 , 120 , 193
Autoantibody rogue B-cell association, 193
Autoantigen, 34–35 , 95 , 99 , 101 , 137 , 165
Autoimmune disease
  CAAR-T cell therapy, 137
  CAR-T cell therapy, 137

causes, 97–104
classification of, 105 , 106t–108t
clinical considerations, 109–111
CRISPR-Cas13, 140
CRISPR-Cas9, 137–140 , 139f
Crohn's disease (CD), 118
diagnosis of, 110–111
environmental factors, 101
epitope spreading, 102–104
etiologies, 98t
female predilection, 95–97
Graves' disease, 123–124
Guillain-Barre syndrome (GBS), 121 , 141–145
immunotherapies, 126–128 , 127t
inflammatory bowel disease (IBD), 116–118
lyonization, 96–97
microbiome, 104
multiple sclerosis (MS), 119–120
myasthenia gravis (MG), 124–125
pathogenesis of, 98t
physical examination, 110
prolonged inflammatory process, 98–99
psoriasis, 122–123
research, 141–145
rheumatoid arthritis (RA), 113–115
signs, 109
symptoms, 109
systemic lupus erythematosus (SLE), 115–116
type 1 diabetes, 120–121 , 141–145
X chromosome inactivation (XCI), 96–97
Autoimmunity, 17–18 , 34–35 , 61 , 73 , 99
Autologous,
hematopoietic stem cell, 134–135
Autologous CAR-T-cell therapy, 137
Autologous transplantation, 134

stem cells, 137

B

B-cell lymphocytes (B 1 , B M), 14f , 19–20 , 54 , 79–80
Base compounds
base pairs, 47f , 55
nucleotide bases, 46 , 138 , 209–210
Basophils, 7–8 , 15 , 132
Big data analytics, 39 , 63 , 212
Bioinformatics, 210–211
Bone marrow transplant, 134 , 141
stem cell transplantation, 131 , 134–135
Brachytherapy, 162
radiation therapy, 162
Breast cancer (BC)
BRCA1, 155
BRCA2, 155

C

C-reactive protein (CRP), 81 , 86 , 113
CAAR-T cell therapy, 165
Calor, 101–102
Cancer
CAAR-T cell therapy, 165
cancering, 151–152
CAR-T cell therapy, 165–168 , 167f
chemotherapy, 162

circuit, 164–165
clinical presentations, 159–161
CRISPR-Cas9, 168
diagnosis, 159–160
epigenetics, 156
etiologies, 155–158
idiotype-anti-idiotype regulatory, 164–165
incidence, 152–154

infectious agents, 156–157
metastasis, 159
microbiome, 156–157
microRNA, 158
molecularly targeted therapies, 163
monoclonal antibodies, 163–164 , 164f
oncoevolution, 156
oncogene, 156
Oncogenesis, 155–156
Oncology, 168–169
p53, 156
prevalence of, 152–154
radiation therapy, 162
random genetic mistakes, 155–156
research, 169–175
treatment considerations, 161–169
types, 153t , 161
X chromosome, 158
Cancering, 151–152
Hillis, Danial, 151–152
CANTOS, 81
CAR-T cell therapy, 165–168
Carcinogen, 155–156
Carcinogenesis, 155–158
Cardio/cerebrovascular diseases, 81
Cas 13 enzyme, gene editing, 140 , 207
Cas 9 enzyme, gene editing, 131–132 , 136–140
Caseation, 76 , 101
Cell-mediated, 15 , 30–31
Central dogma of molecular biology, 51–54 , 53f , 76
protein synthesis, 46–47 , 51–54
Centromere, 47–48
chromosome, 47–48
Checkpoint inhibitor, 87 , 130 , 163–164 , 168 , 188–189
monoclonal antibodies, 128–129

immunotherapy, 80
Chemotherapy, 162
Chimeric, 137 , 138f , 165 , 167f
Chromosome
DNA, 5–6 , 46–51 , 48f , 77 , 99 , 138–139 , 155–156 , 162 , 187 , 197 , 207–208
double helix, 48f
Chronic conditions
chronic disease, 84–86 , 90–91 , 130
chronic inflammation, 71–94
comorbidity, 195
XCI, 96–97
Chronic inflammation
adaptive immune system, *See* Adaptive immune system
advancing adaptive immunity, 73–74
cardio and cerebrovascular diseases, 81
causes (etiologies) of, 72–73
chronic conditions, 85t
chronic inflammatory orthopedic conditions, 83t
clinical diagnosis, 84–87
conditions, 83t
diagnostic strategies, 84–86
disease categories associated with, 80–84
etiologies, 73t
histopathology, 75–77
immune system, neural downregulation of, 87–89
immunotherapies treatment, 86–87
musculoskeletal disease, 82
neurologic and neurodegenerative disease, 82–84
path, 40
pathogenesis, 73t
pathophysiology, 75–77
pharmacodynamics of, 77–80
proinflammatory mediators, 79t
research, 89–91
treatment of, 84–87

Cloning, 136
Clonotypes, 209–210
  nucleotides, 6
Cluster, 10 , 116–117 , 158 , 182–183
  epidemic, 57 , 71–72 , 182–183 , 185
Combination strategies, 168–169
Comorbidity, 195 , 214
  multimorbidity, 210
Computational immunology, 210–211
  immunoinformatics, 210–211
Contact tracing, 199
Convalescent plasma (serum), 201

Corticosteroids, 129–130
COVID-19
  antibody testing, 197
  antigen testing, 196
  antiviral drugs, 202
  clinical considerations for, 194–210
  clinical manifestations, 194–195
  contact tracing, 199
  convalescent plasma, 201
  Coronavirus, 208
  CRISPR-Cas13, 207
  dexamethasone, 201–202
  diagnostic testing, 195–198
  epidemiology, 211–215
  genome sequencing, 197–198
  herd immunity, 209
  human vaccines project, 209
  hydroxychloroquine, 203–204
  immunoinformatics, 210–211
  immunotherapeutics, 199–204
  incidence, 186–188
  Ivermectin, 204
  mitigation, 199

molecular genetic test, 196–197
molnupiravir, 203
monoclonal antibodies, 200–201
mRNA vaccines, 206
prevalence of, 186–188
public health, 213–215
R naught (RO/R O), 209
Remdesivir, 203
research, 215–218
RNA screening, 207
SARS-CoV-2, 71
vaccination (immunization), 208–210
vaccine epitaph, 210
vaccines, 204–208
viral mutations, 187–188
CRISPR-Cas13, Gene editing, 137–140 , 139f
CRISPR-Cas9, Gene editing, 140 , 207
Crohn's disease (CD), 118
Cyclooxygenase, 31–33 , 126–128
inflammatory cascade, 27 , 77–78
Cyclosporine, 140
Cystic fibrosis, 63–65
Cytogenetics, 62–63
Cytokine, 25–26
lymphokine (AU: The term 'Lymphokine' is not found in the chapter text)
Cytokine storm, 188–189
Cytosine (Cs), 46
nucleotide, 209–210

D

Damage-associated molecular patterns (DAMPs), 82
Delta
coronavirus, 197
variant, 187 , 197–198
DeepMind Health, 211
Google, 211

Precision medicine, 56–57 , 109 , 163 , 169–175
Deep learning
algorithms, 233
artificial intelligence (AI), 62–63
Dendritic cell, antigen presenting complex (APC), 11–12 , 12f , 20 , 79–80
Deoxyribonucleic acid (DNA), 46 , 48f , 55–56
Dexamethasone, corticosteroid, 201–202
Diabetes insipidus, 233
Diabetes mellitus, 86 , 195 , 233
Diabetes type 1, 98t , 120–121 , 141–145
Diabetes type 2, 85t
Diapedesis, Endothelial leukocytic adhesion molecule (ELAM), 75–76
Disease-modifying anti-rheumatic drugs (DMARDs), 113–115 , 129
DNA
base compounds, 233
editing, 233
nucleotides, 6 , 46 , 48f , 55 , 209–210
sequencing, 233
structure, 48f , 187
Dolor, acute inflammation, 73–74
Double helix, chromosome, 48–51 , 48f
Down syndrome, 63–65
Downregulate, 87–88
Duchenne muscular dystrophy, 58
Dysbiosis, microbiome, 104 , 156–157
Dysregulation, 25–26

E

Edema, acute inflammation, 32f
Embryonic stem cell (ESC), 132 , 135f
Endemic, 182–183
Endocarditis, 115
Endothelial leukocytic adhesion molecule (ELAM)
diapedesis, 75–76
inflammatory cascade, 31–33
Eosinophils, 132

Epidemic, 71–72

Epidemiology, 181 , 211–215
Epigenetics, 62 , 156
Epigenome, 62
Epitope spreading, Rogue B cells, 102–104
Epitopes, 102–103
Escapees X chromosome inactivation, 96 , 234
Eugenics, 136
Exome, 46
Exon, 48–51
Exposome, 234
Expression, gene, 61 , 95–96 , 156

F

Feedback inhibition, 25–26
Female predilection, autoimmune disease, 95–97
Fever, Leukocytic pyrogen, 101–102
Fibroblast, chronic inflammation, 76
First signal, innate immunity, 13–15
Functio laesa, acute inflammation, 82

G

Gene
  basic science of, 46–54
  big data analytics, 63
  chromosome, 47–48 , 47f
  DNA structure, 48f
  editing, 137–140
  expression, 61 , 96–97 , 137 , 156 , 159–160
  functions, 46–51
  genomics by the numbers, 55–56
  karyotype, 48–51 , 49f
  modulation, 156–157
  molecular biology, central dogma of, 51–54 , 52f–53f
  mutation, 56

replacement therapy, 131
research, 63–65
sequencing, 165 , 197–198
Genetic cloning, 46 , 136
Genetic code, 6 , 16 , 46 , 48 , 55 , 156
Genetic engineering or modification, 136
Genetics, heredity, 46 , 101
Genome, sequencing, 197–198
Genotype, 101
Genomics
big data analytics, 63
by numbers, 55–56
Genotype, 71–72 , 101
Genome, 83–84 , 99
Germline genetic modification, 135–136
Google
DeepMind Health, 211
Precision medicine, 57
Granuloma, chronic inflammation, 76
Graves' disease, 123–124
Guanine (Gs), nucleotide, 138
Guardian of the genome, 55
p53 protein, 156
Guillain-Barre syndrome (GBS), 121 , 141–145

H

Haploid strands, 48–51
Helix, 46–51 , 55–56
Hematopoietic stem cell therapy, 134–135
Herd immunity
COVID-19, 209
pandemic, 190–191
Heredity, genetics, 46 , 51–54 , 101
Heuristic, 63
Hillis, Daniel, Cancering, 151–152
Histamine, 29 , 31–33

Homeostasis, 35 , 61 , 87–88 , 104
Human Genome Project, 3 , 56
Human Immunodeficiency Virus (HIV), acquired immunodeficiency syndrome (AIDS), 185–186
Human Vaccines Project, 209
Humoral, 72 , 78
Hybridoma technology, 128–129
Hydrocortisone, 122–123
Hydroxychloroquine (Plaquenil), 129 , 203–204
Hygiene hypothesis, 60 , 95–96
Hypersensitivity response, 29
Hypertrophy, 159

I

Idiotype Idiotype network theory (INT), 90–91 , 165
Idiotype-anti-idiotype regulatory circuit (Loop), 164–165
Immediate hypersensitivity responses, 29 , 73–74
Immune synapse
  adaptive immune system, *See* Adaptive immune system
  antigen presenting complex (APC), 11–12 , 12f
Immune-complex hypersensitivity, 30
Immunization, 86 , 92 , 208–210
Immunology, 74 , 90–91 , 111–113 , 151–180
  immuno-oncology, 168–169
  immunocompromised, 110 , 154
  immunodeficiency, 185
  immunogenetics, 46 , 54 , 87
  immunogenomics, 16 , 40 , 54–55
  immunoinformatics, 210–211
  immunopharmacology, 129
  immunotherapeutics, 126–128 , 127t
Immunoinformatics, 210–211
Immunome, 76
Immunomodulators, 76 , 209
Immunopathophysiology, 27–31

Immunosenescence, 82
Immunosuppression, 110
Immune system
  active immunity, 9–21
  adaptive immunity, 25–26
  antibody-encoding gene, 16
  antigen presenting complex (APC), 11–12 , 12f
  cellular attack, 15–16
  chemical/humoral attack, 17–18 , 17f
  definition, 87–89
  development of, 87–89
  first signal, 13–15 , 14f
  gross anatomy, 6–7 , 7f
  innate immunity, 9–21
  lyonization, 5–6
  microanatomy, 7–9 , 8f
  molecular biology, 7–9 , 8f
  regulated immune system, 18–20 , 19f
  regulated to dysregulated, 20–21
  research, 21–22
  TLR sentry, 12–13
  X chromosome inactivation (XCI), 5–6
Immunotherapies
  antiviral drugs, 202
  combination strategies, 168–169
  convalescent plasma, 201
  dexamethasone, 201–202
  hydroxychloroquine, 203–204
  Immunotherapies, 126–128
  ivermectin, 204
  molnupiravir, 203
  monoclonal antibodies, 128–129
  Remdesivir, 203
In silico
  computational immunology, 210–211

immunoinformatics, 210–211
InDelphi, 138–139 , 237–238
Induced pluripotent stem cell (iPSC), 132
stem cell transplantation, 131 , 134
Induration, 75–76 , 237–238
chronic inflammation, 71–94
Infectious agents, 156–157
Infiltration, 77
Inflammaging, 82
Inflammation (…itis)
acute inflammation, *See* Acute inflammation
chronic inflammation, *See* Chronic inflammation
Inflammatory bowel disease (IBD), 61 , 116–118
Inflammatory cascade, 78
Inflammatory response, 78
Innate (aka natural) immune response, 72
Insulin, 120
Interferon, 129–130
Interleukins, 204
Isoantigens, Histocompatibility (HLA) gene, 141
Itis, inflammation, 74
Ivermectin, 204

K

Kahler disease, multiple myeloma, 238
Karyotype, chromosomes, 48–51 , 49f , 101 , 238
Kynurenine pathway, 169–175 , 238

L

Leukemia, 161 , 164f , 238
Leukocyte, White blood cell (WBC), 79–80 , 132 , 238
Leukocytic pyrogen, 101–102
calor, 101–102
fever, 109
Ligand
PD 1 and 2, 169

Lipoxygenase, inflammatory cascade, 27
Lymphatic system, 161

Lymphocytes (T H T S T C T M and B B M), 138f
Lymphoma, 156–157
Lyonization (XCI), 58–59 , 96–97
  chromosome, 158

M

Machine learning
  algorithm, 138–139
  artificial intelligence (AI), 141–145
Macrophage, 11 , 82–83
Major histocompatibility complex (MHC), 11–12 , 102–103
MHC Class 1 and 2 genes, 11
Masking effect
  corticosteroids, 36
  dexamethasone, 201–202
Melanoma, 130 , 152–153 , 169
Mendelian disorders
  heredity, 48 , 51
  genetics, 111–113
Messenger RNA (mRNA)
  central dogma of molecular biology, 51–54
  transcription, 189–190
Metastasis, 159
Metastatic cancer, 159
Microanatomy, 7–9
Microbiome, probiotics, 60
Microbiota, 104 , 157
Microchimerism, 5
MicroRNA, X chromosome, 158 , 239–240
Mitigation
  COVID-19, 199
  pandemic, 199
Molecular biology, 7–9 , 135–140

Molecular genetic test, 196–197
Molecularly targeted therapies, 163
Molnupiravir, 203
  Paxlovid, 203 , 241–243
Monoclonal antibodies
  biologics, 129–131
  checkpoint inhibitors, 130
Monocytes, 10 , 30 , 76
mRNA
  central dogma of molecular biology, 51–54
  mRNA screening, 140
  mRNA vaccines, 206
  transcription, 51
Multimorbidity, comorbidity, 86 , 195
Multiple myeloma, 161
Multiple sclerosis (MS), 119–120
Multisystem inflammatory syndrome in children (MIS-C), 105
  cytokine storm, 188–189
Musculoskeletal disease, 82
Mutation, 187–188
  cancer, 152 , 155–156
  DNA, 156–157
Myasthenia gravis (MG), 124–125
Myocarditis, 77 , 115 , 194–195

N

National Cancer Institute, 152
  Precision Medicine Initiaitive, 163
National Institute of Health (NIH), 57 , 74
Natural killer [NK] cells, 7–8 , 19f , 30 , 60
Naught point
  COVID-19, 240
  pandemic, 240
Necrosis, chronic inflammation, 76
Neoadjuvant chemotherapy, cancer, 162
Neoplasm, neoplastic, 71 , 155–156

Neuroendocrine tumors, 161
Neurologic/neurodegenerative disease, 82–84
Neutralizing antibodies, 197
Neutrophils, 132
Next-generation sequencing (NGS), Sanger method, 55
Non-specific therapies, 126
Nonsteroidal anti-inflammatory drugs (NSAIDs), 31–33
Normal flora, 13 , 60
Nuclear factor-kappa B (NF-κB), 88
Nucleic acids, 56
Nucleotide bases, 138

O

Omicron
  coronavirus, 187–188
  variant, 187–188
Omics technologies, 141–145
Oncoevolution, 156
Oncogene, 156
Oncogenesis, 155–156
Oncology, 168–169
Opsinization, adaptive immune system, 241
Organ morphogenesis, 134
Osteoarthritis, 133–134
Outbreak, epidemic, 182–183
Overshoot, herd immunity, 209

P

p53, Guardian of the genome, 156
PALB2, 155
Pandemic
  epidemic, 198
  outbreak, 183
  cluster, 183
Passive immunity, 4

Pathogen, 157
Pathogenesis, 188–193
Pathology, 105
Pathophysiology, 29 , 74–77
Paxlovid, 203
PCR, *See* Polymerase chain reaction (PCR)
PD 1 and 2, ligand, 61 , 130 , 157 , 169
Perivasculitis, 76 , 105 , 188–189
Personalized medicine
  precision medicine, 57
  All of Us, 82 , 158
Phagocytize, 206
Phagocytosis, 15 , 35 , 79–80
Pharmacodynamics, 31–33 , 77–80 , 111
Pharmacoeconomics, 241–243
Pharmacogenetics, 241–243
Pharmacogenomics, 241–243
Pharmacovigilance, 241–243
Phenotype, chromosomes, 99 , 109
Phenotype trigger, 63 , 101 , 109
Phylogeny, 16 , 158 , 193
Plaquenil, hydroxychloroquine, 236
Plasma cells, 16 , 19f , 77 , 102–103 , 161 , 241–243
Platelets, 79–80 , 132
Pluripotent stem cells, stem cell transplantation, 241–243
Polymerase chain reaction (PCR), 191
Polymorphonuclear (PMN), 18–19
Precision (personalized) medicine, National Institute of Health, 74
Precision health
  All of Us, 186–188 , 229–230
  Genetics, 99 , 152
Prevention, 57
Prednisone, 113–115
Prevalence, 84–85 , 152–154 , 186–188
Pro-inflammatory cytokine, 31

Probiotics, microbiome, 60 , 104
Progenitor, 76 , 132–133
Programmed death (PD) protein, 10–11 , 168
  PD-L1, 130 , 169
Proinflammatory mediators, 4 , 78 , 79t , 101–102 , 126
  adaptive immune system, 95–96 , 209–210
Prostaglandins, 88
  inflammatory cascade, 27 , 31–33 , 74 , 78 , 99
Protease, 203
Protein synthesis, 51–52
Proteolysis, 52
Proteome, 215–218
Proteomics, 77
Psoriasis, 106t–108t , 122–123
Public health, 184–185 , 187–188 , 213–215
Pus, 35

R

Radiation therapy, cancer, 162
Radioactive iodine (I-131), 162
Recombinant, vaccines, 202
Regenerative medicine, stem cell transplantation, 132–135
Regulated immune system, 18–20 , 26
Remdesivir, 203
  antiviral, 202
Rheumatoid arthritis (RA), 113–115
Ribonucleic acid (RNA)
  messengerRNA (mRNA), 51–54 , 52f , 205f , 206–207
  microRNA (miRNA), 61 , 158
  transferRNA (tRNA), 51–54
Ribosome, 51
RNA
  RNA Ribonucleic acid, 46–47
  RNA screening, 207
  RNA sequencing (scRNA-seq), 137
  RNA structure, 48f

R-Naught (R O or RO), 209
Rogue B cell, 102–105 , 193
  epitope spreading, 101–105
Rubor, acute inflammation, 35–36 , 73–74

S

Sanger method, Next gen sequencing, 55
Sarcoma, 161
SARS-CoV-2, COVID-19, 181 , 188–193
  genetic and genomic considerations, 192–193
  life cycle, 189–190 , 189f
  mechanisms, 188–189

  natural pathogenesis, 191–192
  novel coronavirus, 181
  pathogenesis, 188–193
  theories, 190–191
Sequences, 47f , 55–56 , 137 , 158 , 184
Seroconversion, 191
Serology, 191
Serotype (Ad5), 206 , 208
Serum, Plasma, 201
Small-molecule drugs, 163
Social distancing, 212–213
  COVID-19, 184–185
Somatic cells, 8–9
Somatic mutations, 63–65
Spike protein, 187 , 189f , 192 , 204
  novel coronavirus, 181 , 184–185 , 191–192 , 206
Staging, cancer, 161
Stem cell therapy, regenerative medicine, 132–135
Stem cell transplantation, 131 , 134
Stress antigens, 99
Subgenomic RNA, SARS-CoV-2, 189f
Systemic Lupus Erythematosus (SLE), 105 , 115–116

T

T-cell lymphocytes (T H T S T C T M), 132

T-cell transfer therapy, 165

  CAR-T therapy, 165–168

Telomere, chromosome, 245–246

Thrombocytes, 245–246

Thymine (Ts)

  nucleotide, 240

  base compound, 231

TIDE. *See* Tumor Immune Dysfunction and Exclusion (TIDE)

TLR sentry, 12–13

Tumor Necrosis Factor alpha (TNF-α), 245–246

Toll-like receptors (TLRs), 21–22

  sentry of the immune system, 21–22

Topoisomerase inhibitors, 103–104

Transcription, Central dogma of molecular biology, 245–246

Transcriptomics, 52

Transfer RNA (tRNA), 51

Translation, Central dogma of molecular biology, 245–246

Transplant therapies, 134 , 140–141

tRNA Transfer RNA, 51

Tumor

  cancer, 85t

  acute inflammation, 32f

Tumor necrosis factor (TNF), 78 , 81 , 129–130

Type 1 diabetes, 120–121

Type 2 diabetes, 85t

U

Ulceration, 99

Uracil, 46–47

  base compound, 246

Urticaria, 246

V

Vaccination, 200–201

Vaccination (immunization), 208–210
Vaccine, 204–208
  CRISPR-Cas13, 207
  mRNA vaccines, 204–208
  recombinant, 206
  RNA screening, 207
Vaccine epitaph, 210
Variants
  Delta, 187
  mutation, DNA, 187
  Omicron, 187–188
Vasculitis, 246
Vasodilation, inflammation, 246
Viral mutations, 187–188

W

White blood cell (WBC), leukocyte, 8f , 10 , 132 , 201
Whole-exome sequencing (WES), 55 , 246
Whole-genome sequencing (WGS), 246

X

X chromosome, miRNA, 225
X chromosome inactivation (XCI), 5–6 , 96–97 , 158

Z

Zoonotic spillover, 191–192 , 247